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(54) Title  
NEW CEPHALOSPORINS CONTAINING, IN POSITION 3, A PROPENYL RADICAL SUBSTITUTED BY  
A QUARTERNARY AMMONIUM, THEIR PREPARATION PROCESS, THEIR USE AS MEDICAMENTS,  
THE COMPOSITIONS CONTAINING THEM AND THE INTERMEDIATES OBTAINED

(51)<sup>5</sup> International Patent Classification(s)  
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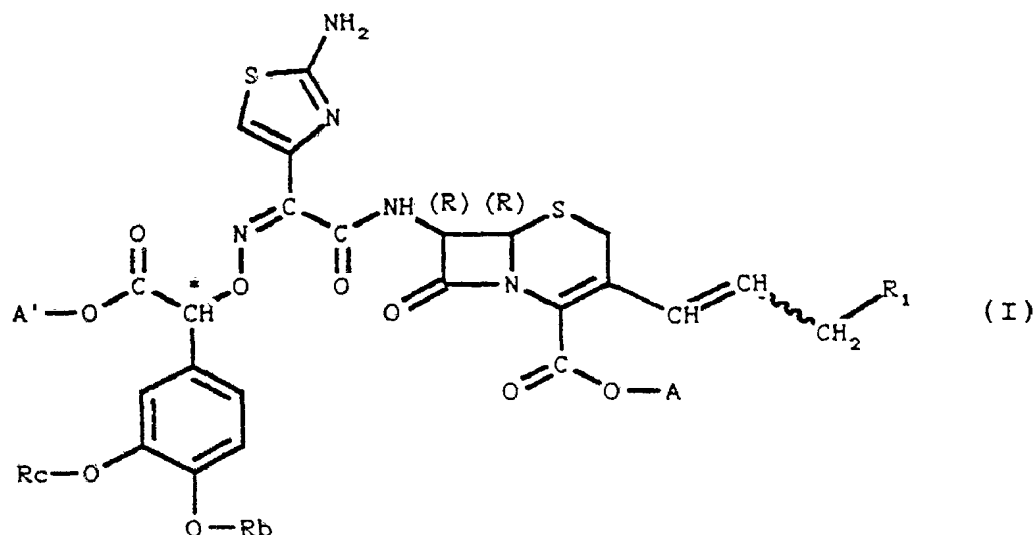
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(56) Prior Art Documents  
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GB 2134522  
GB 2157293

(57) Claim

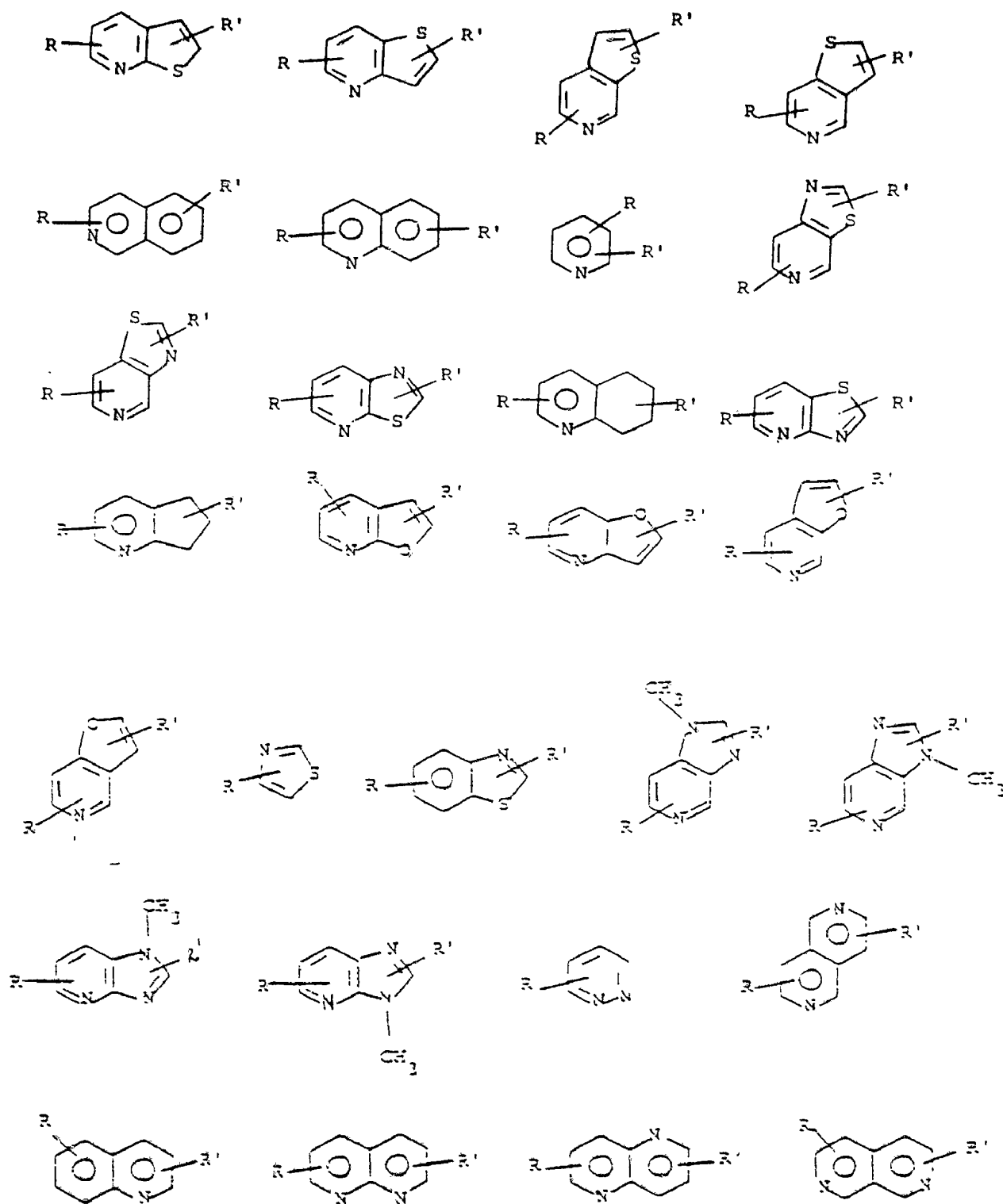
1.- The products of general formula (I):



SYN isomer

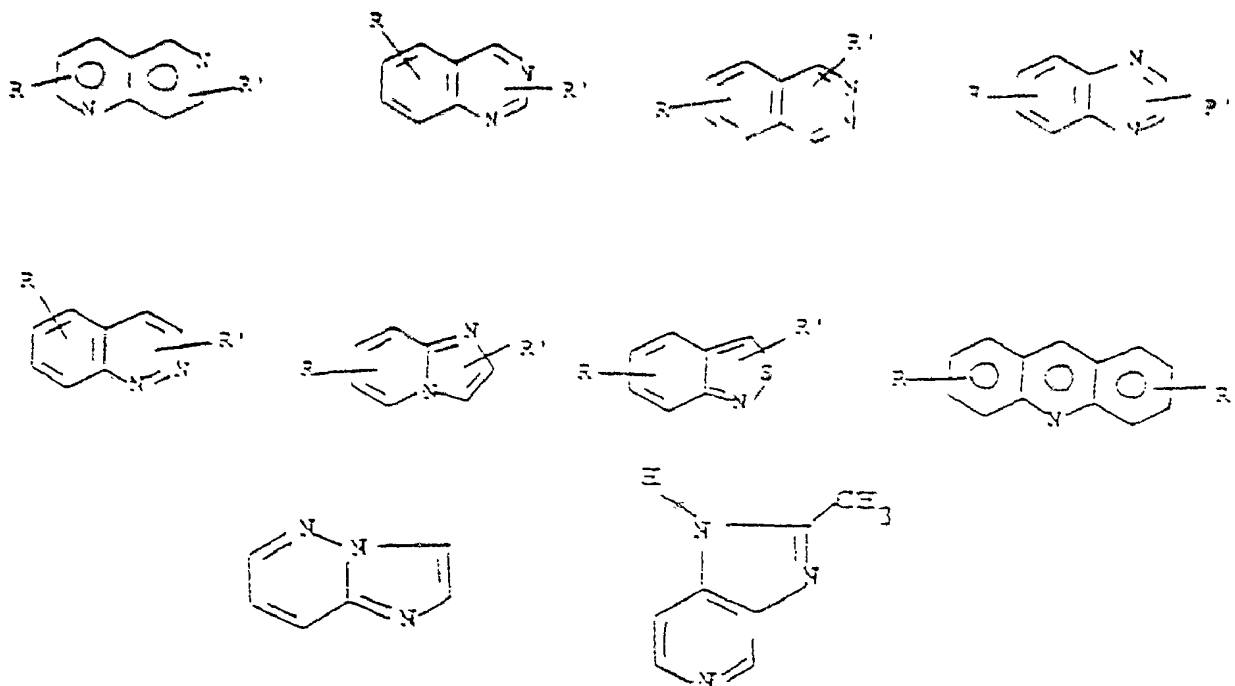
syn isomer, in R or S form or in the form of an R, S, mixture, formula in which:

R<sub>1</sub> represents a radical chosen from the following radicals: <sub>2</sub>



(11) AU-B-78370/91  
(10) 643289

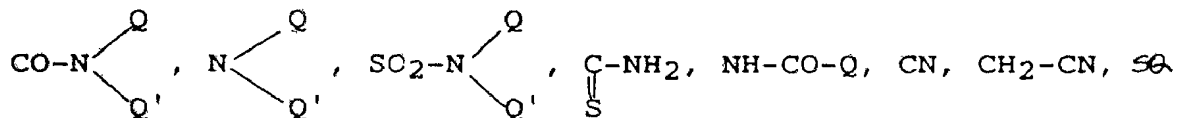
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or in the quaternary ammonium form or



in which R and R', identical or different, represent a hydrogen atom, an alkyl radical containing 1 to 4 carbon atoms, an alkoxy radical containing 1 to 4 carbon atoms, a halogen atom, one of the following radicals a CO<sub>2</sub>-Q,



CH<sub>2</sub>-SQ in which Q and Q', identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, P, P' and P'', identical or different, represent an alkyl radical containing at most 4 carbon atoms, optionally substituted by one of the substituents indicated above for R and R', the symbol indicating that P and P' can optionally form, with the nitrogen atom to which they are linked, a saturated heterocycle with 5 or 6 links.

(11) AU-B-78370/91

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$R_b$  and  $R_c$ , identical or different, represent a hydrogen atom or an acyl group,

A and A', identical or different, represent a hydrogen atom, an equivalent of an alkali metal, an alkaline-earth metal, magnesium, ammonium or an amino organic base or A and A' represent the remainder of an easily cleavable ester group or  $CO_2A$  represents  $CO_2^-$ ; the wavy line means that the  $CH_2R_1$  group can be found in E or Z position as well as the salts of the products of formula (I) with the mineral or organic acids.

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

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Int. Cl:

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Related Art:

TO BE COMPLETED BY APPLICANT

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Complete Specification for the invention entitled: **NEW CEPHALOSPORINS CONTAINING, IN POSITION 3, A PROPENYL RADICAL SUBSTITUTED BY A QUATERNARY AMMONIUM, THEIR PREPARATION PROCESS, THEIR USE AS MEDICAMENTS, THE COMPOSITIONS CONTAINING THEM AND THE NEW INTERMEDIATES OBTAINED.**

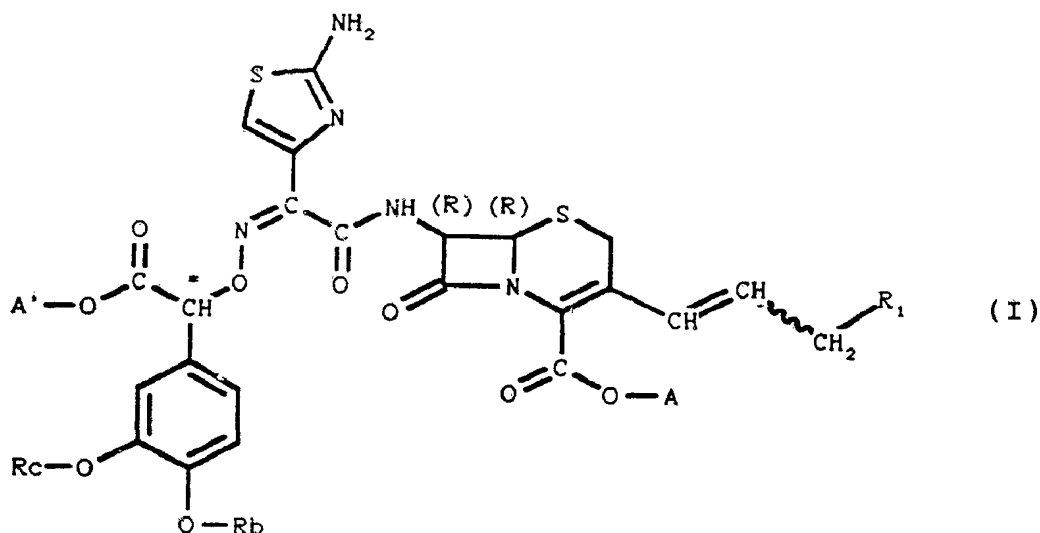
The following statement is a full description of this invention, including the best method of performing it known to me:-

1a

New cephalosporins containing, in position 3, a propenyl radical substituted by a quaternary ammonium, their preparation process, their use as medicaments, the compositions containing them and the new intermediates obtained.

The present invention relates to new cephalosporins containing, in position 3, a propenyl radical substituted by a quaternary ammonium, their preparation process, their use as medicaments, the compositions containing them and the new intermediates obtained.

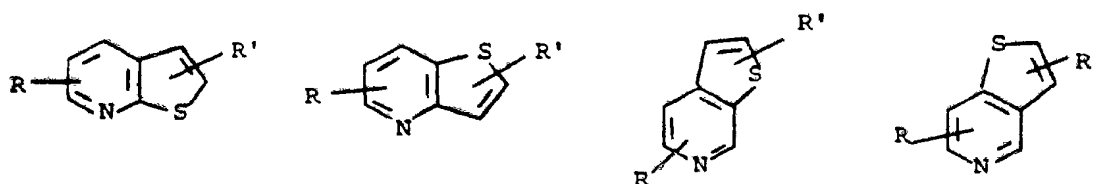
A subject of the invention is the products of general formula (I):

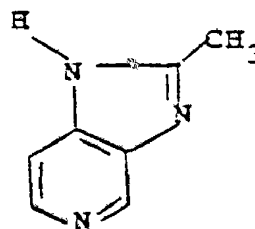
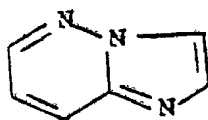
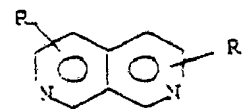
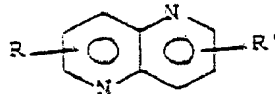
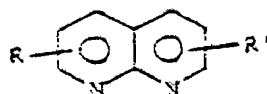
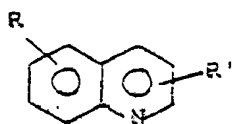
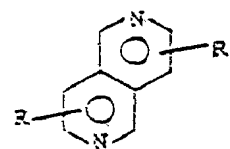
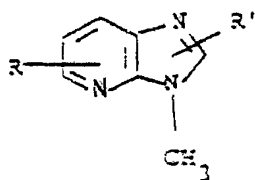
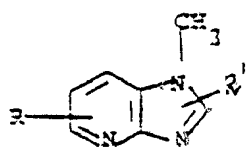
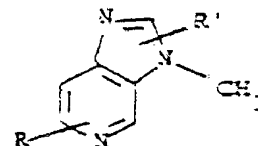
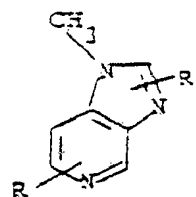
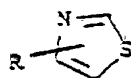
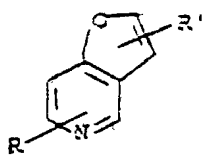
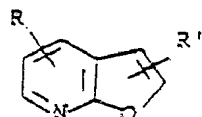
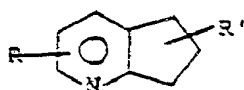
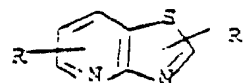
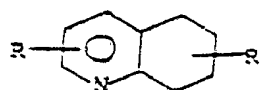
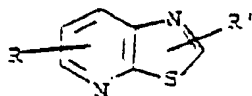
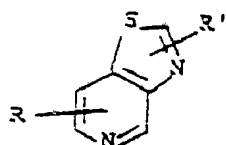
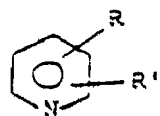
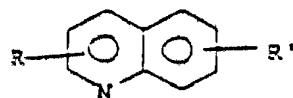
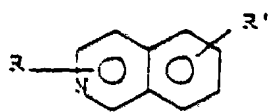


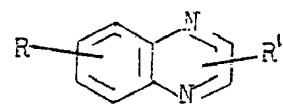
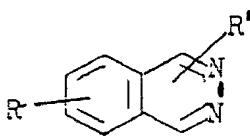
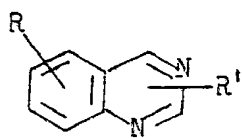
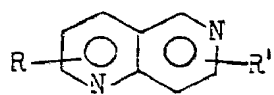
SYN isomer

syn isomer, in R or S form or in the form of an R, S, mixture, formula in which:

R<sub>1</sub> represents a radical chosen from the following radicals:



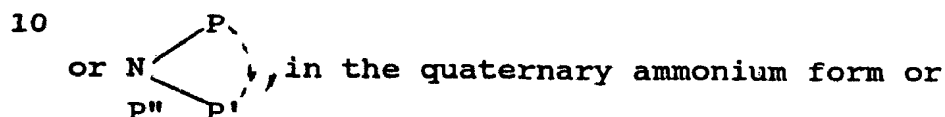
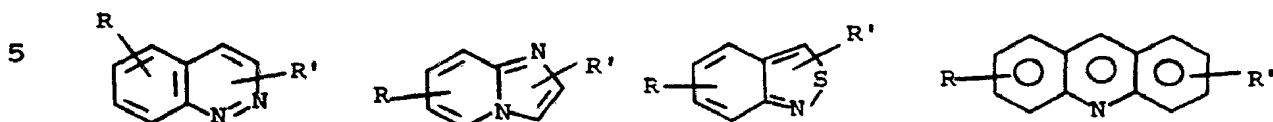




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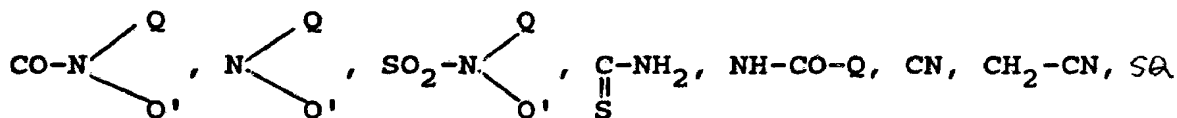


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20 in which R and R', identical or different, represent a hydrogen atom, an alkyl radical containing 1 to 4 carbon atoms, an alkoxy radical containing 1 to 4 carbon atoms, a halogen atom, one of the following radicals a  $\text{CO}_2\text{-Q}$ ,

25



30  $\text{CH}_2\text{-SQ}$  in which Q and Q', identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, P, P' and P'', identical or different, represent an alkyl radical containing at most 4 carbon atoms, optionally substituted by one of the substituents indicated above for R and R', the symbol indicating that P and P' can optionally form, with the nitrogen atom to which they are linked, a <sup>saturated</sup> heterocycle with 5 or 6 links.

35  $\text{R}_b$  and  $\text{R}_c$ , identical or different, represent a hydrogen atom or an acyl group,

A and A', identical or different, represent a hydrogen atom, an equivalent of an alkali metal, an alkaline-earth metal, magnesium, ammonium or an amino organic base or A and A'



represent the remainder of an easily cleavable ester group or  $\text{CO}_2\text{A}$  represents  $\text{CO}_2^-$ ; the wavy line means that the  $\text{CH}_2\text{R}_1$  group can be found in E or Z position as well as the salts of the products of formula (I) with the mineral or organic acids.

5 By alkyl radical containing 1 to 4 carbon atoms, is meant, for example, methyl, ethyl, propyl, isopropyl, butyl, linear or branched.

When P and P' form a heterocycle with the nitrogen atom to which they are linked, it can be a pyrrolidine, a  
10 morpholine or a piperidine.

When  $\text{R}_b$  and/or  $\text{R}_c$  represent an acyl radical, it can be an acetyl, propionyl or benzoyl radical. It can also be the other acyl value mentioned hereafter. The preferred acyl value is the acetyl value. The preferred value for  $\text{R}_b$  and  $\text{R}_c$  is the  
15 hydrogen value.

Among the values of A and A' there can be mentioned an equivalent of sodium, potassium, lithium, calcium, magnesium or ammonium. Among the organic bases there can be mentioned methylamine, propylamine, trimethylamine, diethylamine,  
20 triethylamine, N,N-dimethylethanolamine, tris[(hydroxymethyl)-amino]-methane, ethanolamine, pyridine, picoline, dicyclohexylamine, morpholine, benzylamine, procaine, lysine, arginine, histidine, N-methylglucamine.

Among the other remainders of easily cleavable ester  
25 groups that can be represented by A and A', the following groups can be mentioned: methoxymethyl, ethoxymethyl, isopropoxyloxyethyl, alpha-methoxy ethyl, alpha-ethoxy ethyl, methyl-thiomethyl, ethylthiomethyl, isopropylthiomethyl, pivaloyloxyethyl, acetoxymethyl, propionyloxyethyl,  
30 butyryloxyethyl, isobutyryloxyethyl, valeryloxyethyl, isovaleryloxyethyl, tert-butylcarbonyloxyethyl, hexadecanoyloxyethyl, propionyloxyethyl, isovaleryloxyethyl, 1-acetyloxy-ethyl, 1-propionyloxyethyl, 1-butyryloxyethyl, 1-tertbutylcarbonyloxyethyl, 1-acetyloxypropyl, 1-hexadecanoyl-  
35 oxyethyl, 1-propionyloxypropyl, 1-methoxycarbonyloxyethyl, methoxycarbonyloxyethyl, 1-acetyloxybutyl, 1-acetyloxyhexyl, 1-acetyloxyheptyl, phthalidyl, 5,6-dimethoxyphthalidyl, tert-butylcarbonylmethyl, allyl, 2-chloroallyl,

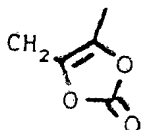
methoxycarbonylmethyl, benzyl or tert-butyl.

Among the other remainders of ester groups that can be represented by A and A', the following groups can be mentioned: methoxyethoxymethyl, dimethylaminoethyl,

- 5 cyanomethyl, tert-butoxycarbonylmethyl, 2,2-ethylenedioxyethyl, cyanoethyl, 2,2-dimethoxyethyl, 2-chloroethoxymethyl, 2-hydroxyethoxy-ethyl, 2,3-epoxypropyl, 3-dimethylamino, 2-hydroxypropyl, 2-hydroxyethyl, 2-methylaminoethoxymethyl, 2-aminoethoxymethyl, 3-methoxy-2,4-  
10 thiadiazol-5-yl, 2-tetrahydropyrannyl, 1-methoxy-1-methylethyl, 2-hydroxy-1-methyl-ethyl, isopropyl, carbamoylmethyl, chloromethyl, 2-chloroethyl, acetylmethyl, 2-methylthioethyl or thiocyanatomethyl.

Among the other remainders of ester groups that can be

- 15 represented by A and A', the following groups can be mentioned: 2-chloro-1-acetyloxyethyl, 2-bromo-1-acetyloxyethyl, 2-fluoro-1-acetyloxyethyl, 2-methoxy-1-acetyloxyethyl, 2-methyl-1-acetyloxypropyl, 1-methyl-1-acetyloxyethyl, 1-methoxyacetyloxyethyl, 1-  
20 acetylcarbonyloxyethyl, 1-hydroxyacetyloxyethyl, 1-formylcarbonyloxyethyl, 1-(2-thienyl)-carbonyloxyethyl, 1-(2-furyl)-carbonyloxyethyl, 1-(5-nitro-2-furyl)-carbonyloxyethyl, 1-(2-pyrrolyl)-carbonyloxyethyl, 1-(propionyloxycarbonyloxy)-ethyl, 1-(propyloxycarbonyloxy)-ethyl, 1-  
25 (isopropyloxycarbonyloxy)-ethyl, 1-(methoxyethoxycarbonyloxy)-ethyl, 1-(allyloxycarbonyloxy)-ethyl, isopropyloxycarbonylmethyl, 1-[(2,3-epoxypropyl)-oxycarbonyloxy]-ethyl, 1-[(2-furyl)-methyloxycarbonyloxy]-ethyl, 1-(2-fluoro-ethyl)-oxycarbonyloxyethyl, 1-(methoxycarbonyloxy)-propyl, 1-  
30 (methoxycarbonyloxy)-1-methyl-ethyl, (methoxycarbonyloxy)-chloromethyl, 1-(methoxycarbonyloxy)-2-chloroethyl, 1-(methoxycarbonyloxy)-2-methoxy-ethyl, 1-(methoxycarbonyloxy)-allyl, or a remainder



The products of formula (I) can also be presented in the form of organic or mineral acid salts.

Among the acids with which the amino group or groups of products (I) can be salified, there can be mentioned among  
5 others the following acids: acetic, trifluoroacetic, maleic, tartaric, methanesulphonic, benzenesulphonic, paratoluenesulphonic, phosphoric, sulphuric, hydrochloric, hydrobromic, hydroiodic.

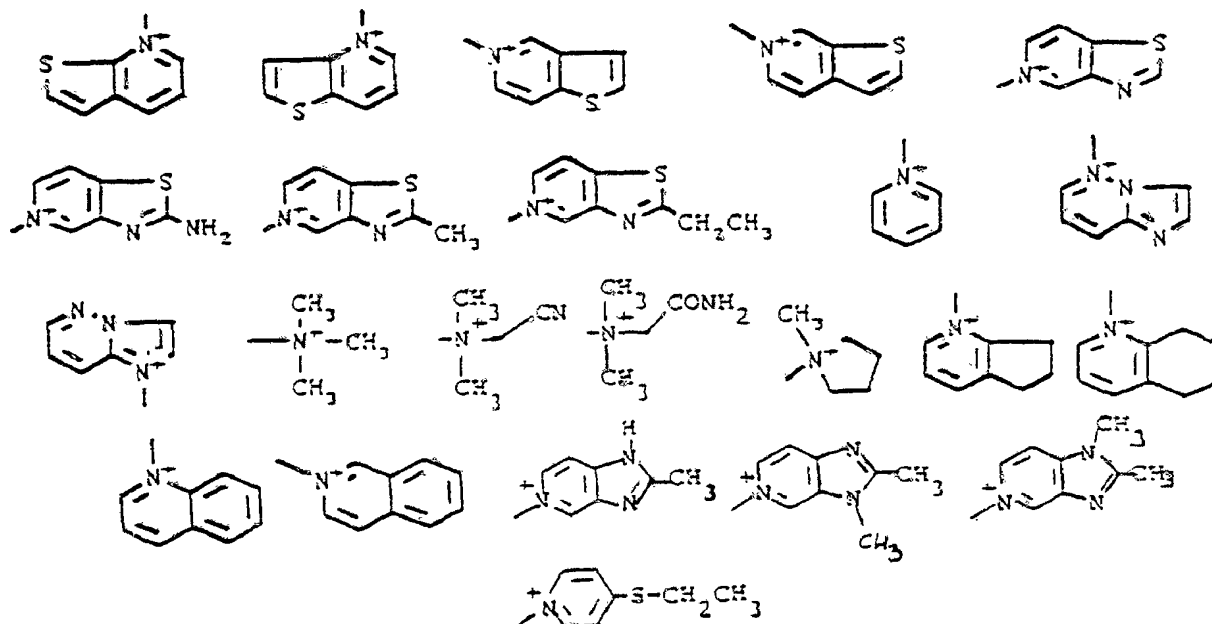
10 The products can also be presented in the form of internal salts.

In a preferred method of the invention, A' represents a hydrogen or sodium atom, preferably hydrogen and CO<sub>2</sub>A represents CO<sub>2</sub> ⊖.

15 The expression in the form of quaternary ammonium indicates that the R<sub>1</sub> radical is linked by the nitrogen atom or one of the nitrogen atoms that it contains.

Particularly a subject of the invention is the products of general formula (I) as defined above in which R<sub>1</sub> is chosen from the following radicals:

20.

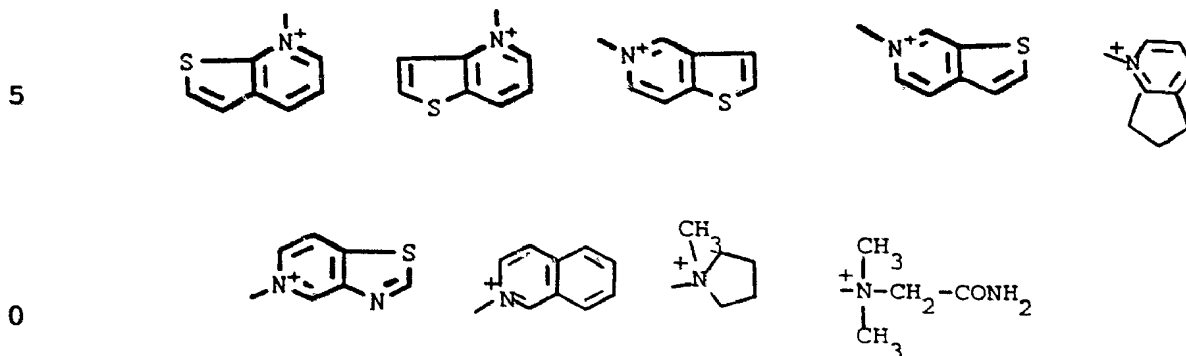


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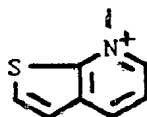
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More particularly a subject of the invention is the

products of general formula (I) as defined above in which R<sub>1</sub> is chosen from the following radicals:



preferably the radical:



Quite particularly a subject of the invention is the products described hereafter in the examples, namely:

- [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-

[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thiazolo-[4,5-c]-pyridinium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with

alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,

- [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-

[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b] pyridinium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters and particularly in the S form,

- [6R-[3(E), 6alpha, 7beta(Z)]]-2-[3-[7-[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-

[4,2,0]-oct-2-en-3-yl]-2-propenyl] isoquinolinium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,

- [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-1-methyl pyrrolidinium in

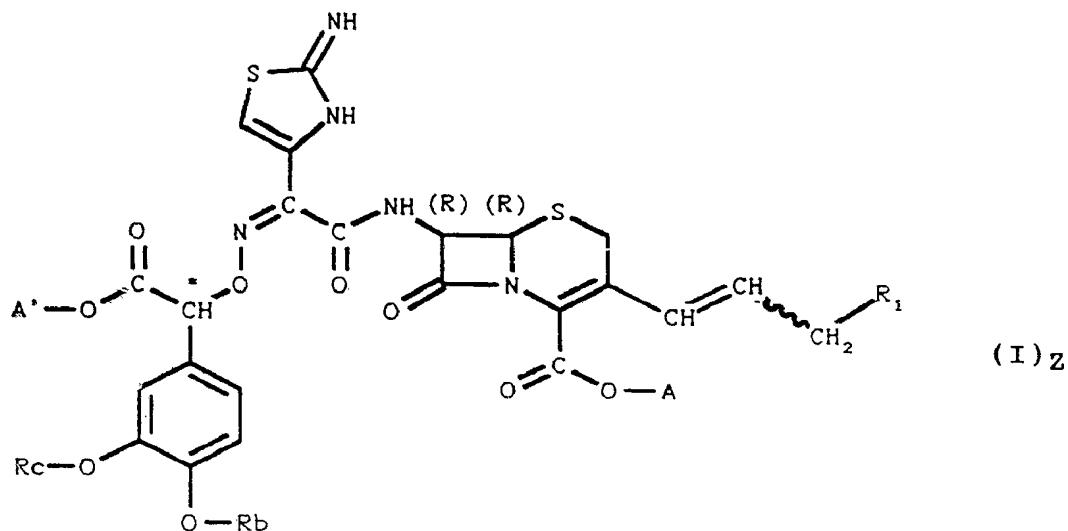
the R or S form or the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,

- [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-6,7-dihydro-5H-pyrimidinium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,

- [6R-[3(E), 6alpha, 7beta(Z)]]-N-(2-amino-2-oxoethyl)-3-[7-[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N,N-dimethyl-2-propen-1-aminium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters.

It is understood that the aforementioned products of formula (I) can exist:

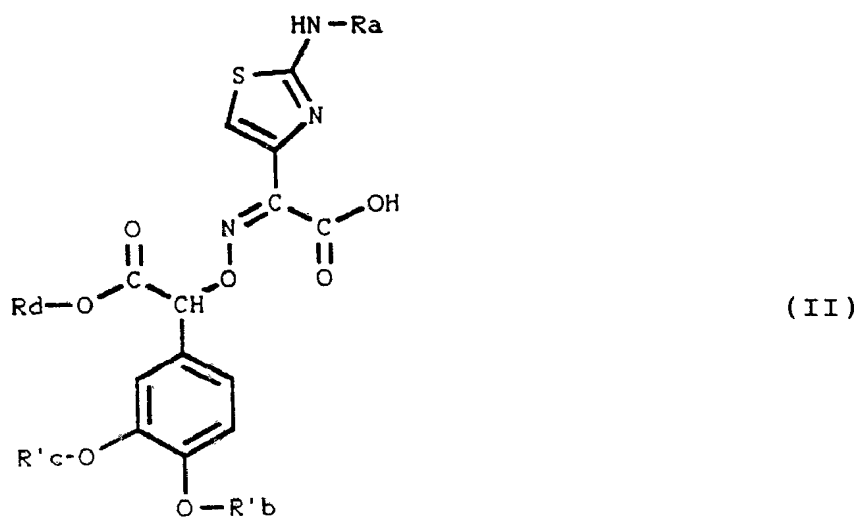
either in the form indicated by said formula (I),  
or in the form of products of formula (I)<sub>2</sub>:



SYN isomer

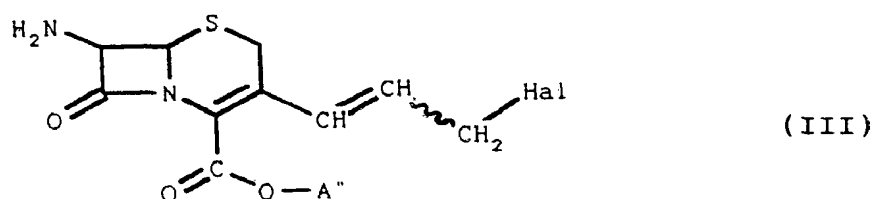
in which A, A', R<sub>1</sub>, R<sub>b</sub> and R<sub>c</sub> have the previous meaning.

Also a subject of the invention is a preparation process for the products of formula (I) as defined above, characterized in that a product of formula (II):

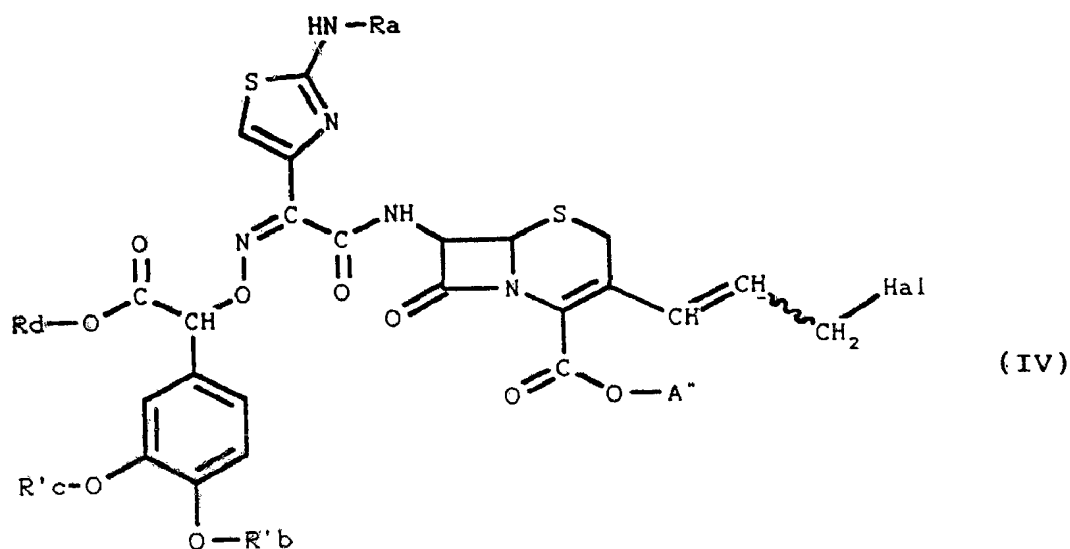


racemic or optically active syn isomer or a functional

derivative of the product of formula (II), in which  $R_a$  represents a hydrogen atom or a protective group of the amino radical,  $R'_b$  and  $R'_c$ , identical or different, represent a hydrogen atom or a protective group of the hydroxyl radical,  $R_d$  represents a hydrogen atom or the remainder of an easily eliminable ester group, is reacted with a product of formula (III):



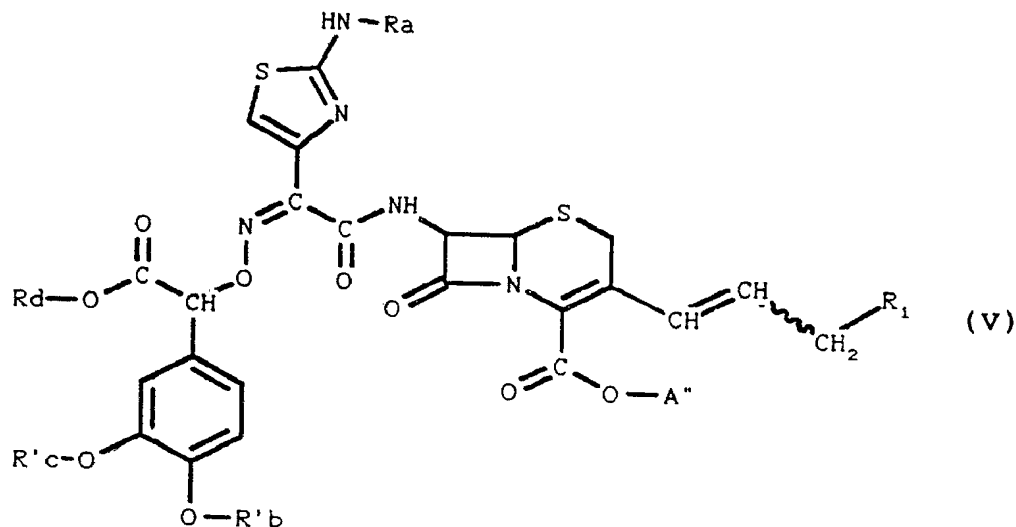
15 in which Hal represents a halogen atom,  $A''$  represents a hydrogen atom or the remainder of an easily eliminable ester group and the wavy line indicates that the  $CH_2Hal$  group can be found in E or Z position, in order to obtain a product of formula (IV):



35 which is reacted with a reagent capable of introducing the  $R_1$



radical in order to obtain a product of formula (V):



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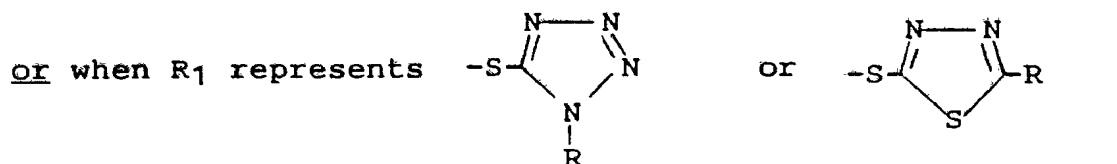
which, if desired, is separated into its E or Z isomers or the Z isomers are converted into E isomers and which products of formula (V), if necessary or if desired, are subjected to one or more of the following reactions, in any order:

- 25
- 30
- cleaving, by hydrolysis or by the action of the thiourea, of all or part of the ester groups or protective groups of the amino radical or the hydroxyl radicals,
  - esterification or salification of the carboxylic radical or radicals by a base,
  - salification of the amino radical by an acid,
  - separation of products in the form of an R, S mixture into R or S.

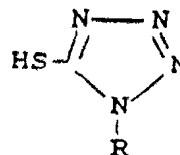
By reagent capable of introducing the R<sub>1</sub> radical, is meant:

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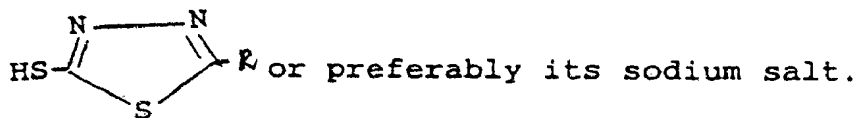
either when R<sub>1</sub> represents a quaternary ammonium, a reagent composed of the R<sub>1</sub> radical itself, this not being in the form of quaternary ammonium; notably if one wishes to introduce a pyridinium radical, the operation will be done with pyridine,



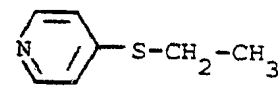
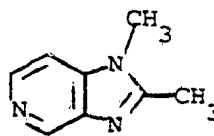
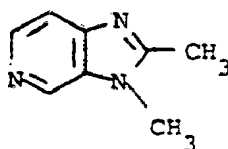
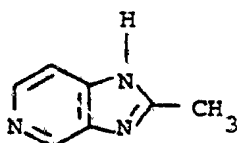
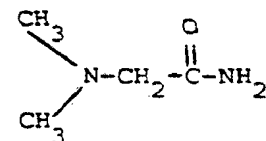
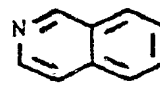
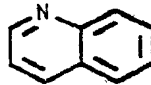
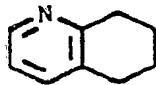
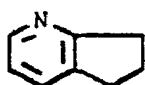
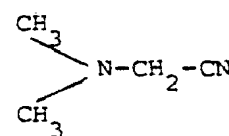
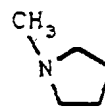
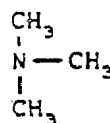
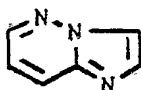
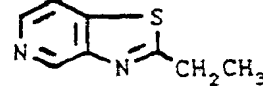
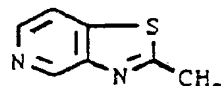
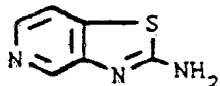
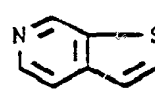
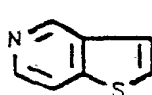
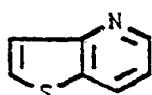
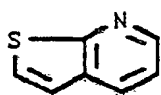
a reagent corresponding respectively to



or



Among the preferred reagents, there can also be mentioned those corresponding to the formulae:



In addition to the groups mentioned above, the easily eliminable ester groups which can be represented by A'' and R<sub>d</sub> can be for example the ester formed with the following radicals: butyl, isobutyl, tert-butyl, pentyl, hexyl, acetoxymethyl, propionyloxymethyl, butyryloxymethyl, valeryloxymethyl, pivaloyloxymethyl, 2-acetoxyethyl, 2-propionyloxyethyl, 2-butyryloxyethyl.

The following radicals can also be mentioned: 2-

iodoethyl, 2,2,2-trichloroethyl, vinyl, allyl, ethynyl, propynyl, benzyl, 4-methoxybenzyl, 4-nitrobenzyl, phenylethyl, trityl, diphenylmethyl, 3,4-dimethoxyphenyl.

The following radicals can also be mentioned: phenyl, 4-5 chlorophenyl, tolyl, tert-butylphenyl.

The diphenylmethyl radical is preferred for  $R_d$  and the 4-methoxybenzyl or diphenylmethyl radical is preferred for A".

The protective group of the amino radical which can be represented by  $R_a$  can be for example, an alkyl radical with 10 to 6 carbon atoms such as, preferably, tert-butyl or tert-amyl.

$R_a$  can also represent an aliphatic, aromatic or heterocyclic acyl group or a carbamoyl group. The lower alkanoyl groups can be mentioned, such as for example, formyl, 15 acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, oxalyl, succinyl, pivaloyl.

$R_a$  can also represent a lower alkoxy or cycloalkoxycarbonyl group, such as for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, 1-20 cyclopropylethoxycarbonyl, isopropylloxycarbonyl, butyloxycarbonyl, tert-butylloxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, a benzoyl, toluoyl, naphthoyl, phthaloyl, mesyl, phenylacetyl, phenylpropionyl group, an aralkoxycarbonyl group, such as benzyloxycarbonyl.

25 The acyl groups can be substituted, for example, by a chlorine, bromine, iodine or fluorine atom. The following radicals can be mentioned: chloroacetyl, dichloroacetyl, trichloroacetyl, bromoacetyl or trifluoroacetyl.

$R_a$  can also represent a lower aralkyl group such as 30 benzyl, 4-methoxybenzyl, phenylethyl, trityl, 3,4-dimethoxybenzyl or benzhydryl.

$R_a$  can also represent a haloalkyl group such as trichloroethyl.

$R_a$  can also represent one of the following groups: 35 chlorobenzoyl, para-nitrobenzoyl, para-tert-butylbenzoyl, phenoxyacetyl, caprylyl, n-decanoyl, acryloyl, trichloroethoxycarbonyl.

Ra can also represent a methyl carbamoyl, phenylcarbamoyl, naphthylcarbamoyl group, as well as the corresponding thiocarbamoyls.

The trityl group is preferred.

5 The above list is not limitative, it is obvious that other amine protective groups, in particular groups known in the chemistry of peptides, can also be used.

10 The protective group of the hydroxyl radicals which can be represented by R'b and R'c, can be chosen from the list below:

R'b and R'c can represent an acyl group, such as for example, formyl, acetyl, propionyl, chloroacetyl, bromoacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, benzoyl, benzoylformyl, p-nitrobenzoyl. The following groups can also be mentioned: ethoxy carbonyl, methoxycarbonyl, propoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, benzyloxycarbonyl, tert-butoxycarbonyl, 1-cyclopropylethoxycarbonyl, tetrahydropyrannyl, tetrahydrothiopyrannyl, methoxytetrahydropyrannyl, trityl, benzyl, 4-methoxybenzyl, benzhydryl, trichloroethyl, 1-methyl-1-methoxyethyl, phthaloyl.

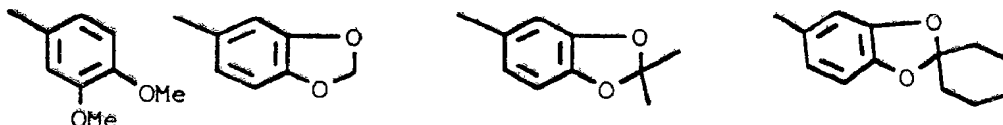
Other acyls can also be mentioned such as butyryl, isobutyryl, valeryl, isovaleryl, oxalyl, succinyl and pivaloyl.

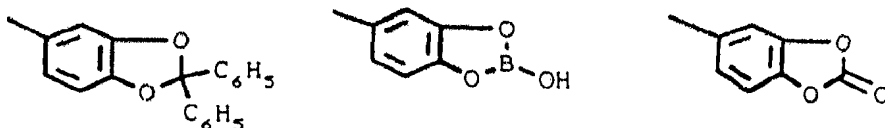
The following radicals can also be mentioned: phenylacetyl, phenylpropionyl, mesyl, chlorobenzoyl, para-nitrobenzoyl, para-tert-butylbenzoyl, caprylyl, acryloyl, methylcarbamoyl, phenylcarbamoyl, naphthylcarbamoyl.

30 The following radicals can also be mentioned: alkoxy alkoxy methyl, such as methoxy ethoxy methyl.

The OR'b and OR'c radicals can also form with the phenyl radical to which they are linked, the following values:

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The methoxy ethoxy methyl group is preferred for substituents R'<sub>b</sub> and R'<sub>c</sub>.

10 In a method for implementing the process, a functional derivative of the product of formula (II) is reacted. This functional derivative can be for example, a halide, a symmetrical or mixed anhydride, an amide, an azide or an activated ester.

As an example of a mixed anhydride there can be mentioned, for example, that formed with isobutyl chloroformate and that formed with pivaloyl chloride and the carboxylic-sulphonic mixed anhydrides formed, for example, with the paratoluene sulphonyl chloride.

As an example of an activated ester, there can be mentioned the ester formed with 2,4-dinitrophenol and that formed with hydroxybenzothiazole.

As an example of the halide, there can be mentioned the chloride or bromide.

The anhydride can be formed in situ by action of N,N'-disubstituted carbodiimide, for example N,N'-dicyclohexylcarbodiimide.

The acylation reaction preferably takes place in an organic solvent such as methylene chloride. However others solvents such as tetrahydrofuran, chloroform or dimethylformamide can be used.

When an acid halide is used and in a general manner when an acid halide molecule is released during the reaction, the reaction is preferably carried out in the presence of a base such as soda, potash, sodium or potassium carbonates and acid carbonates, sodium acetate, triethylamine, pyridine, morpholine or N-methylmorpholine.

The reaction temperature is, in general, lower or equal to ambient temperature.

Also a product of formula (II) can be reacted directly with a product of formula (III) in the presence of a carbodiimide such as diisopropylcarbodiimide. An example of such a preparation is given further on in the experimental 5 part.

The action of the reagents capable of introducing the  $R_1$  radical onto the product of formula (IV) is carried out in the following conditions:

When Hal represents, for example, a chlorine atom, a 10 substitution of the chlorine atom by an iodine atom, in the presence of sodium iodide, can be carried out in situ or separately, then the desired reagent is added, either in the presence or not of an organic solvent such as acetonitrile or tetrahydrofuran. Examples of such reactions are described 15 hereafter in the experimental part.

The desired reagent can also be reacted, in the presence of silver tetrafluoroborate, on the product of formula (IV) in which Hal represents a chlorine atom. An example of such a preparation is also to be found in the experimental part.

20 The isomerism of the products of formula (V) can be different to that of the products of formula (IV) used at the start. In the case where the Z isomer is isolated, this isomer can be converted into the E isomer according to usual methods, notably by the action of iodine.

25 According to the values of  $R_a$ ,  $R'_b$ ,  $R'_c$ ,  $R_d$  and  $A''$ , the products of formula (V) can or cannot constitute the products of formula (I).

The products of formula (V) constitute the products of formula (I) when  $R_a$  represents a hydrogen atom, when  $R'_b$  and 30  $R'_c$  do not represent a protective group of the hydroxyl radical that one wishes to eliminate, namely when  $R'_b$  and/or  $R'_c$  represent an acyl radical and when  $R_d$  and  $A''$  do not represent, among the easily cleavable ester groups, one of those that one would wish to eliminate.

35 In the other cases, the action on the product of formula (V) of one or more hydrolysis agents, hydrogenolysis agents or thiourea has the object of eliminating the  $R_a$  radical when

this represents a protective radical of the amino radical, of eliminating the  $R'_b$  and  $R'_c$  radicals when these represent a protective group of the hydroxyl radicals and/or of eliminating the  $R_d$  and  $A''$  radicals when these represent, among  
 5 the easily cleavable ester groups one of those that one wishes to eliminate.

However, it is of course possible to eliminate  $R_a$ ,  $R'_b$  and  $R'_c$  without touching substituents  $R_d$  and  $A''$  when these must be preserved. This is the case, for example, when  $A''$   
 10 represents an ester group that one wishes to preserve, such as a propionyloxymethyl group.

The nature of the reagents brought into play in such a case is well known to a man skilled in the art. Examples of such reactions are given further on in the experimental part.

15 For example, a description of the various elimination methods of the different protective groups will be found in the French Patent Application B.F. 2,499,995.

Given that the preferred protective groups used are: trityl for  $R_a$ , methoxy ethoxy methyl for  $R'_b$  and  $R'_c$ ,  
 20 diphenylmethyl for  $R_d$  and 4-methoxybenzyl or diphenylmethyl for  $A''$ , trifluoroacetic acid without a solvent or in a solvent such as anisole or a mixture of solvents such as anisole/methylene chloride is preferably used. A salt is then obtained with trifluoroacetic acid. Return to the free base  
 25 can be effected by the action of a base such as triethylamine carbonate.

The salification of the products can be carried out according to usual methods.

Salification can, for example, be obtained by the action  
 30 of a mineral base such as sodium or potassium hydroxide, sodium or potassium carbonate or acid carbonate, on a product in acid form or on a solvate, for example, the ethanolic solvate or hydrate of this acid. Mineral acid salts such as trisodium phosphate can also be used. Organic acid salts can  
 35 also be used.

As organic acid salts, there can be mentioned, for example, sodium salts of aliphatic, linear or branched,

saturated or unsaturated carboxylic acids with 1 to 18 carbon atoms and preferably with 2 to 10 carbon atoms. The aliphatic chains of these acids can be interrupted by one or more heteroatoms such as oxygen or sulphur or substituted by aryl radicals, such as, for example: phenyl, thienyl, furyl, by one or more hydroxyl radicals or by one or more halogen atoms such as fluorine, chlorine or bromine, preferably chlorine, by one or more carboxylic or lower alkoxy carbonyl radicals, preferably methoxycarbonyl, ethoxycarbonyl or propyloxycarbonyl, by one or more aryloxy radicals, preferably phenoxy.

Furthermore, as organic acids, sufficiently soluble aromatic acids can be used, such as, for example, substituted benzoic acids preferably substituted by lower alkyl radicals.

As examples of such organic acids, the following acids can be mentioned:  
 formic, acetic, acrylic, butyric, adipic, isobutyric, n-caproic, isocaproic, chloropropionic, crotonic, phenylacetic, 2-thienylacetic, 3-thienyl-acetic, 4-ethylphenylacetic, glutaric, the monoethylic ester of adipic acid, hexanoic, heptanoic, decanoic, oleic, stearic, palmitic, 3-hydroxypropionic, 3-methoxypropionic, 3-methylthiobutyric, 4-chlorobutyric, 4-phenylbutyric, 3-phenoxybutyric, 4-ethylbenzoic, 1-propylbenzoic.

However sodiumacetate, sodium 2-ethyl hexanoate or sodium diethyl acetate are preferably used as sodium salts.

Salification can also be obtained by the action of an organic base such as triethylamine, diethylamine, trimethylamine, propylamine, N,N-dimethyl ethanolamine, tris[(hydroxymethyl)-amino] methane, methylamine, ethanolamine, pyridine, picoline, dicyclohexyl amine, morpholine and benzylamine.

It can also be obtained by the action of arginine, lysine, procaine, histidine, N-methyl glucamine. This salification is preferably carried out in a solvent or a mixture of solvents such as water, ethyl ether, methanol, ethanol or acetone.

The salts are obtained in amorphous or crystallized form



according to the reaction conditions employed.

Crystallized salts are prepared preferably by reacting free acids with one of the salts of the aliphatic carboxylic acids mentioned above, preferably, with sodium acetate.

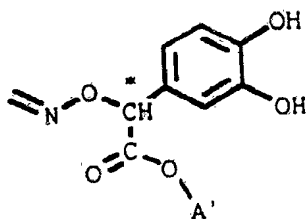
- 5 The salification of products by mineral or organic acids is carried out in the usual conditions.

The optional esterification of products is carried out in standard conditions. The operation is done, in general, by reacting the acid of formula (I) or a functional derivative  
10 with a derivative of formula:



in which Z represents a hydroxyl radical or a halogen atom  
15 such as chlorine, bromine, iodine and Re designates the ester group to be introduced, a non-exhaustive list of which groups is given above. In some cases, it can be advantageous to carry out an esterification on a product whose amine and/or reaction groups which are present on the oxyimino are blocked before  
20 removing the protective group of the amine and the reaction group which are present on the oxyimino.

The products of formula (I) comprise several asymmetrical carbons. In the cepheme nucleus, which comprises two asymmetrical carbons, the two carbon are in R configuration.  
25 Furthermore the radical present on the oxyimino function also comprises an asymmetrical carbon:



30

which can be in R or S form or in the form of an R, S mixture.  
35 The separation of the two diastereoisomers can be carried out by ways known to a man skilled in the art, for example, by chromatography.

The products of general formula (I) have a very good

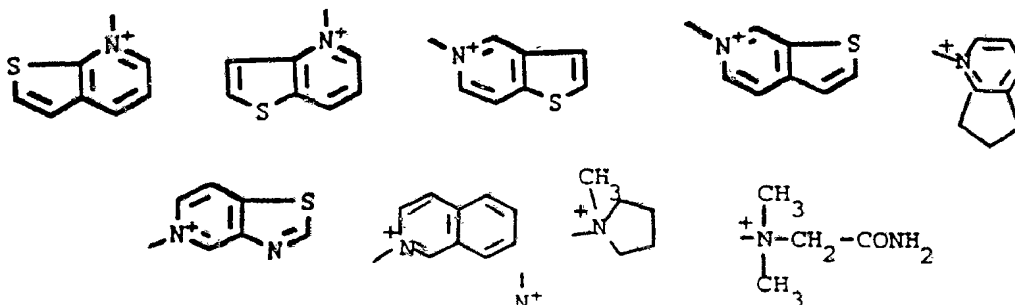
antibiotic activity on gram (+) bacteria such as staphylococcus, streptococcus and notably on penicillin-resistant staphylococcus. Their effectiveness on gram (-) bacteria notably on coliform bacteria, klebsiella, salmonella, proteus and pseudomonas, is particularly remarkable.

These properties render said products, as well as their salts of pharmaceutically acceptable acids, suitable to be used as medicaments in the treatment of affections caused by sensitive germs and notably in that of staphylococcus, such as staphylococcus septicemia, malignant staphylococcus of the face or skin, pyodermitis, septic or suppurating wounds, anthrax, phlegmons, erysipelas, acute primitive or post-influenza staphylococcus, bronchopneumonia, lung suppurations.

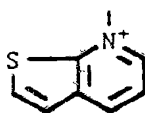
These products can also be used as medicaments in the treatment of colibacillosis and associated infections, in infections due to proteus, klebsiella and salmonella and in others affections caused by gram (-) bacteria.

Therefore a subject of the present invention is also, as medicaments and notably antibiotic medicaments, the products of formula (I) as defined above as well as their salts with pharmaceutically acceptable acids.

More particularly a subject of the invention is as medicaments, the products of formula (I) as described above in which R<sub>1</sub> is chosen from the radicals:



preferably the radical:



Especially a subject of the invention is, as medicaments and notably antibiotic medicaments, the products described hereafter in the examples, namely:

- [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[2-amino-4-thiazolyl)-[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thiazolo-[4,5-c] pyridinium  
 5 in R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with pharmaceutically acceptable alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,

10 - [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[2-amino-4-thiazolyl)-[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b] pyridinium  
 in R or S form or in the form of an R, S mixture and in the  
 15 form of an internal salt or a salt with pharmaceutically acceptable alkali metals, alkaline-earth metal, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters and particularly in the S form,

- [6R-[3(E), 6alpha, 7beta(Z)]]-2-[3-[7-[[2-amino-4-thiazolyl)-[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl] isoquinolinium in R or S  
 20 form or in the form of an R, S mixture and in the form of an internal salt or a salt with pharmaceutically acceptable  
 25 alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,

- [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[2-amino-4-thiazolyl)-[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-1-methyl pyrrolidinium in R  
 30 or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with pharmaceutically acceptable alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,

35 - [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[2-amino-4-thiazolyl)-[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-6,7-dihydro-5H pyridinium



in R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with pharmaceutically acceptable alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable  
5 esters,

- [6R-[3(E), 6alpha, 7beta(Z)]]-N-(2-amino-2-oxoethyl)-3-[7-  
[[ (2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-  
oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-  
1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N,N-dimethyl-2-propen-1-  
10 aminium in R or S form or in the form of an R, S mixture and  
in the form of an internal salt or a salt with  
pharmaceutically acceptable alkali metals, alkaline-earth  
metals, magnesium, ammonia, amino organic bases, acids and its  
easily cleavable esters.

15 The invention extends to pharmaceutical compositions  
containing, as active ingredient, at least one of the  
medicaments defined above.

These compositions can be administered by buccal, rectal,  
parenteral route, notably intramuscular or local route as a  
20 topical application on the skin and mucous membranes.

The products of formula (I) and notably those in which A  
represents a cleavable ester can be administered by oral  
route.

The pharmaceutical compositions according to the  
25 invention can be solid or liquid and be presented in the  
pharmaceutical forms currently used in human medicine, such as  
for example, plain or sugar-coated tablets, capsules,  
granules, suppositories, injectable preparations, ointments,  
creams, gels; they are prepared according to the usual  
30 methods. The active ingredient or ingredients can be  
incorporated with excipients usually employed in these  
pharmaceutical compositions, such as talc, gum arabic,  
lactose, starch, magnesium stearate, cocoa butter, aqueous or  
non-aqueous vehicles, fatty substances of animal or vegetable  
35 origin, paraffin derivatives, glycols, various wetting,  
dispersing or emulsifying agents, preservatives.

These compositions can notably be presented in the form  
of a powder intended to be dissolved extemporaneously in an

appropriate vehicle, for example, apyrogenic sterile water.

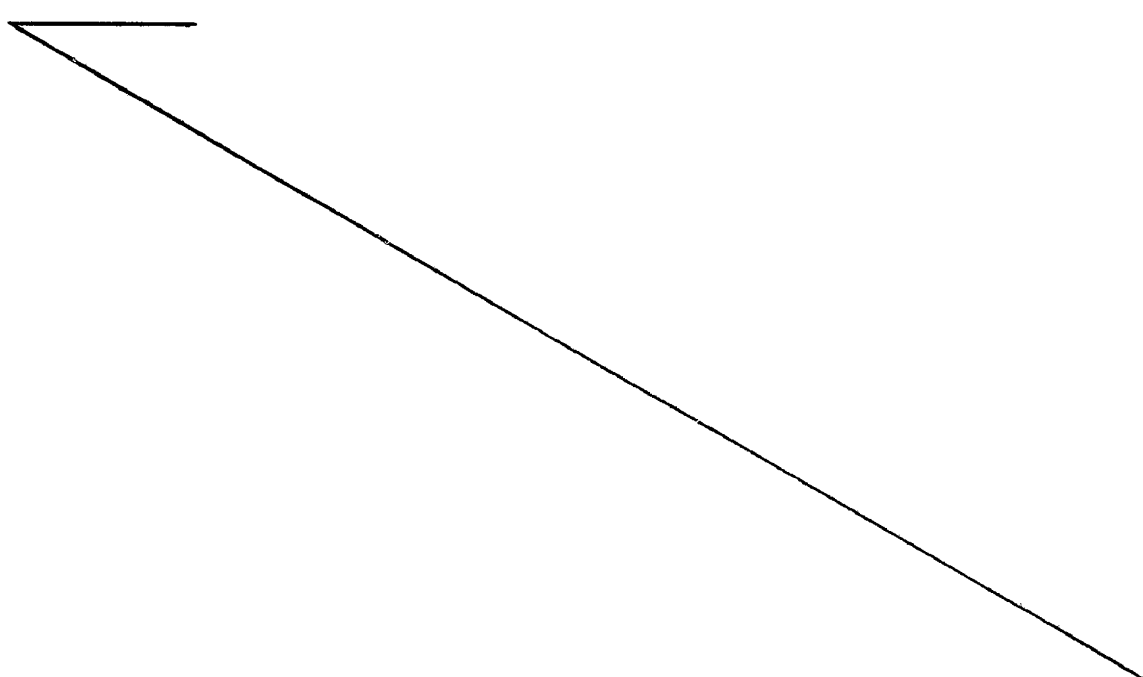
The dose administered is variable according to the affection treated, the subject in question, the administration route and the product used. It can be, for example, comprised 5 between 0.250 g and 4 g per day, by oral route for an adult, for the product described in Example 1 or also comprised between 0.500 g and 1 g three times per day by intramuscular route.

The products of formula (I) can also be used as 10 disinfectants for surgical instruments.

Finally a subject of the invention is, as new industrial products and notably as intermediate products necessary for the preparation of the products of formula (I) as defined above, the products of formula (IV) and the products of 15 formula (V) in which  $R_a$  represents a protective group of the amino radical, formulae (IV) and (V) being as defined above.

The products of formula (II) are known from the literature, notably in the European Patent Application EP 0,238,061 or EP 0,266,060 or can be prepared according to 20 usual methods.

The products of formula (III) are also known from the literature, notably in the British Patent Application GB 2,134,522 or the German Patent DE 3512225.



The following examples illustrate the invention without however limiting it.

**EXAMPLE 1:** [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[2-amino-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b] pyridinium trifluoroacetate tetrafluoroborate

**STAGE A:** [6R-[3(E), 6alpha, 7beta(Z)]]-diphenylmethyl-7-[[[1-[3,4-bis-(2-methoxy-ethoxy)-methoxy]-phenyl]-2-(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-3-(3-chloro-1-propenyl)-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-ene-2-carboxylate.

0.372 cm<sup>3</sup> of diisopropylcarbodiimide in 1 cm<sup>3</sup> of methylene chloride is added to a mixture of 1.876 g of [[3,4-bis-(2-methoxy-ethoxy)-methoxy]-phenyl]-(diphenyl-methoxy-carbonyl)-methoxy]-imino]-[2-(triphenyl-methyl-amino)-4-thiazolyl] acetic acid syn isomer, described in the European Patent EP 238061, 0.955 g of diphenylmethyl-7-amino-3-(3-chloro-1-propenyl)-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-ene-2-carboxylate described in the German Patent DE 35 12 225 and 200 cm<sup>3</sup> of dried methylene chloride.

Agitation takes place for 45 minutes then the solvent is evaporated off under reduced pressure and the residue is chromatographed on silica (eluant: methylene chloride 87.5 - ethyl acetate 12.5).

2.1 g of a yellow product is obtained (R<sub>f</sub> = 0.42 thin layer chromatography, eluant: methylene chloride -ethyl acetate (8-2)).

Infrared

30 = C-NH	3402 cm <sup>-1</sup>
	1792 cm <sup>-1</sup> beta lactame
$\text{>C=O}$	1731 cm <sup>-1</sup> ester
	1683 cm <sup>-1</sup> secondary amide
C=C	1594 cm <sup>-1</sup>
35 +	1584 cm <sup>-1</sup>
Aromatic	1525 cm <sup>-1</sup>
+	1517 cm <sup>-1</sup>
Secondary amide	1396 cm <sup>-1</sup>

## Ultraviolet

1) In EtOH + 1 cm<sup>3</sup> CHCl<sub>2</sub>

infl 217 nm epsilon = 74300

infl 238 nm epsilon = 35500

5 infl 271 nm epsilon = 20800

infl 296 nm epsilon = 16400

2) In EtOH + HCl 0.1 N

infl 217 nm epsilon = 76400

infl 239 nm epsilon = 28800

10 max 283 nm epsilon = 26200

infl 271, 291 and 305 nm.

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[[1-[3,4-bis-  
 [(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenyl-methoxy)-2-  
 oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-  
 15 acetyl]-amino]-2-[(diphenylmethoxy)-carbonyl]-8-oxo-5-thia-1-  
 azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b]-  
 pyridinium tetrafluoroborate

A mixture of 55.9 mg of silver tetrafluoroborate, 38.8  
 mg of thieno-[2,3-b]-pyridine and 5 cm<sup>3</sup> of methylene chloride  
 20 is treated with ultrasonics, then 136 mg of the product  
 obtained in Stage A slightly diluted in methylene chloride is  
 added and agitation takes place for 1 h 15.

After filtering and evaporating, the residue is taken up  
 in ether, a solid is obtained which is washed with 3 times 3  
 25 cm<sup>3</sup> of ether and 207 mg of product is obtained which is  
 purified by chromatography on silica (eluant: methylene  
 chloride - methanol). The fractions are evaporated and 62 mg  
 of product is obtained. R<sub>f</sub> = 0.28 thin layer chromatography  
 (eluant: methylene chloride - methanol (9:1)).

## 30 Ultraviolet

1) In EtOH

max 238 nm epsilon = 368

infl 287 nm epsilon = 168

max 300 nm epsilon = 184

35 2) In EtOH, HCl 0.1 N

infl 236 nm epsilon = 333

max 293 nm epsilon = 209

STAGE C: [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7- [(2-amino-4-

thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b]-pyridinium trifluoroacetate tetrafluoroborate

5 The following two solutions are mixed together at 0°C:

- a) 0.180 g of product obtained in stage B, 4.3 cm<sup>3</sup> of methylene chloride and 0.86 cm<sup>3</sup> of anisole,
- b) 8.6 cm<sup>3</sup> of trifluoroacetic acid and 4.3 cm<sup>3</sup> of methylene chloride, and agitation takes place for one hour at 0°C.

10 After evaporating and the product obtained is taken up in ether solidified. After filtering and washing with ether 100.6 mg of product is obtained which is placed in 3.3 cm<sup>3</sup> of a trifluoroacetic acid solution with 10% of anisole.

Agitation takes place for one hour at 0°C, followed by  
15 evaporating then precipitating the product in ether. After filtering and rinsing 87.9 mg of expected product is obtained.

**EXAMPLE 2:** [6R-[3(E), 6alpha, 7beta(2)]]-7-[3-[7-[[2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-  
20 [4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b] pyridinium in the form of an internal salt

A mixture of 89.4 mg of the product obtained as in Example 1, 2.84 cm<sup>3</sup> of acetonitrile and 2.84 cm<sup>3</sup> of a 0.1N solution of triethylamine carbonate is eluted on an RP 18  
25 silica column with a CH<sub>3</sub>CN-H<sub>2</sub>O (50-50) mixture. The useful fractions are lyophilized and 50.8 mg of expected product is obtained.

Infrared (Nujol)

Beta lactame	1770 cm <sup>-1</sup>
30 Other C = O's	1675 cm <sup>-1</sup>
	approx. 1598 cm <sup>-1</sup>

Ultraviolet, in EtOH, HCl 0.1 N

max	240 nm	epsilon = 28600
max	290 nm	epsilon = 24000

35 **EXAMPLE 3:** [6R-[3(E), 6alpha, 7beta(2)]]-5-[3-[7-[[2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thiazolo-[4,5-c] pyridinium



**trifluoroacetate iodide**

**STAGE A:** [6R-[3(E), 6alpha, 7beta(Z)]]-diphenylmethyl-7-[[[1-[3,4-bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-3-(3-iodo-1-propenyl)-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-ene-2-carboxylate.

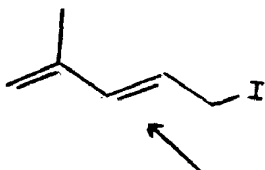
A mixture of 650 mg of product obtained in Stage A of Example 1, 19.1 cm<sup>3</sup> of acetone and 216.3 mg of sodium iodide is agitated for 2 hours at ambient temperature, the solvent is evaporated off then the residue is taken up in 26.5 cm<sup>3</sup> of ethyl acetate.

The solution is washed with 3 times 15 cm<sup>3</sup> of sodium thiosulphate then with 2 times 15 cm<sup>3</sup> of water.

After drying on magnesium sulphate, filtering, rinsing, evaporating, the residue is taken up in a methylene chloride - ethyl acetate (7-3) mixture, 5.3 g of silica is added, agitation takes place for 5 minutes followed by filtering and rinsing.

445 mg of product is obtained after evaporation (Rf = 0.54 on thin layer chromatography, eluant methylene chloride - ethyl acetate (7-3)).

NMR in CDCl<sub>3</sub>



ppm: 6.09 (dm J = 16)

6.12 (dm J = 16)

**STAGE B:** [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[[1-[3,4-bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(diphenylmethoxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thiazolo-[4,5-c]-pyridinium iodide

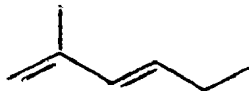
A mixture of 445.2 mg of the product obtained in Stage A in the smallest possible quantity of dimethylsulphoxide and 48.2 mg of thiazolo-[4,5-c] pyridine is agitated for 5 hours, then the solvent is eliminated under reduced pressure.

The viscous residue is washed with 3 times 7 cm<sup>3</sup> of ether. 374.6 mg of a solid is obtained which is purified on silica (eluant: methylene chloride - methanol (92-8)).

24 mg of product having the Z isomer, 21.2 mg of an E+Z mixture and 154.3 mg of product having the E isomer are obtained. (R<sub>f</sub> = 0.18 on thin layer chromatography, eluant: methylene chloride - methanol (9-1)).

NMR (CDCl<sub>3</sub>)

10



6.50 ppm 1H

STAGE C: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thiazolo-[4,5-c]-pyridinium trifluoroacetate iodide

A mixture of the two following solutions is agitated for one hour at 0°C:

a) 238.6 mg of product obtained in Stage B, 5.7 cm<sup>3</sup> of methylene chloride and 1.14 cm<sup>3</sup> of anisole and

b) 11.4 cm<sup>3</sup> of trifluoroacetic acid in 5.7 cm<sup>3</sup> of methylene chloride.

The solvents are evaporated off then the product is precipitated in ether. After filtering and washing, 0.124 g of product is obtained which is mixed with 4.14 cm<sup>3</sup> of trifluoroacetic acid and 0.46 cm<sup>3</sup> of anisole. Agitation takes place for 40 minutes maintaining the temperature at 0°. After evaporating the product is then precipitated in ether. After filtering, rinsing with ether and drying 95.8 mg of expected product is obtained.

EXAMPLE 4: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thiazolo-[4,5-c]-pyridinium in the form of an internal salt

A solution of 95 mg of the product obtained in Example 3, 3.6 cm<sup>3</sup> of acetonitrile and 3.8 cm<sup>3</sup> of triethylamine carbonate

is passed through an RP18 silica column. The column is eluted with a mixture of acetonitrile-water (50-50). The useful fractions are lyophilized and 63.8 mg of expected product is obtained.

5 Ultraviolet, in EtOH, HCl 0.1 N

max 225 nm epsilon = 38500

max 286 nm epsilon = 23500

infl 274, 300 and 356 nm

Infrared (Nujol)

10  $\text{>O}$  1770  $\text{cm}^{-1}$  Beta lactame  
1676  $\text{cm}^{-1}$  complex  
Aromatic region 1626  $\text{cm}^{-1}$   
 $\text{COO}^{\ominus}$  1596  $\text{cm}^{-1}$   
Secondary amide 1536  $\text{cm}^{-1}$

15 **EXAMPLE 5:** [6R-[3(E) 6alpha, 7beta(Z)]]-4-[3-[[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2(E)-propenyl]-thieno-[3,2-b]-pyridinium trifluoroacetate tetrafluoroborate.

20 **STAGE A:** 6R-[3(E) 6alpha, 7beta(Z)]]-4-[3-[7-[[[3,4-bis-[(2-methoxyethoxy)-methoxy]-phenyl]-2-[(diphenyl-methoxy)-2-oxoethoxy]-imino]-[2-(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(diphenylmethoxy)-carbonyl-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2(E)-propenyl]-thieno-[3,2-b]-pyridinium tetrafluoroborate.

The operation is carried out as in Stage B of Example 1 starting with 1.2 g of the product prepared as indicated in Stage A of Example 1, 346 mg of silver fluoroborate in 44  $\text{cm}^3$  of methylene chloride and 0.24  $\text{cm}^3$  of thieno-[3,2-b]-pyridine and after chromatography on silica (eluant: methylene chloride - methanol 92-8 then 96-4) 337 mg of expected product is obtained.

NMR ( $\text{CDCl}_3$  300 Hz)

-CH=CH-CH<sub>2</sub>- : 6.23 (dm, J=16) delta E

35 -CH=CH-CH<sub>2</sub>- : 5.44 (m)

the CH's of the thienyl : 7.67 (d, resolved) 8.25 (d, resolved)

the CH's of the pyridine : 7.76 (m), 8.74 (d, resolved), 8.93 (d, resolved)

**STAGE B:** [6R-[3(E) 6alpha, 7beta(Z)]]-4-[3-[[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2(E)propenyl]-thieno-[3,2-b]-pyridinium 5 trifluoroacetate tetrafluoroborate.

The operation is carried out as in Stage C of Example 1 starting with 316.1 mg of the product obtained above in Stage A, 1.51 cm<sup>3</sup> of anisole in 7.5 cm<sup>3</sup> of methylene chloride and 13.7 cm<sup>3</sup> of trifluoroacetic acid in 7.5 cm<sup>3</sup> of methylene chloride. 183 mg of product is obtained, to which another 6.3 cm<sup>3</sup> of trifluoroacetic acid with 10% anisole is added and agitation is continued for 1 hour at 0°C. The solvent is evaporated off, the residue is taken up in ether, the precipitate is filtered, washed with ether and dried under reduced pressure. 124.1 mg of expected product is collected.

NMR (DMSO)

$\text{=N-O-}\overset{\text{H}}{\text{CH}}\text{-CO}_2\text{H}$  : 5.33 (s)  
 $\text{-CH-S}$  : 5.15 (d)

20 N

$\text{S-CH}_2\text{-}$  : 3.49 (m) partially masked  
 $\text{-CH=}\overset{\text{H}}{\text{CH}}\text{-CH}_2$  : 6.33 (dt, J=5 and 8) delta E  
 $\text{-H=}\overset{\text{H}}{\text{CH}}\text{-CH}_2$  : 5.72 (m)

25 N  $\overset{\text{H}_7}{\oplus}\text{-CH}_2$

phenyl

H<sub>5</sub> thiazole : 6.57 to 7.07

mobile H

30 H<sub>6</sub>', H<sub>3</sub>', H<sub>2</sub>', H<sub>7</sub>', H<sub>5</sub>' of thienopyridine : 8.04 to 9.36

**EXAMPLE 6:** [6R-[3(E) 6alpha, 7beta(Z)]]-4-[3-[[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2(E)-propenyl]-thieno-[3,2-b]-pyridinium trifluoroacetate tetrafluoroacetate.

**STAGE A:** [6R-[3(E), 6alpha, 7beta(Z)]]-diphenylmethyl-7-[[[1-[3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-(diphenyl-methoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-

thiazolyl]-acetyl]-amino]-3-(3-iodo-1-propenyl)-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-ene-2-carboxylate.

The operation is carried out as in Stage A of Example 3 using 3 g of the chlorinated product obtained in Stage A of Example 1 in 100 cm<sup>3</sup> of acetone and 1.0 g of sodium iodide. 3.3 g of iodinated derivative identical to that obtained in Example 3 is obtained which is used as it is in the following stage.

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-4-[3-[7-[[[1-[3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(diphenylmethoxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[3,2-b]-pyridinium iodide.

The operation is carried out as in Stage B of Example 3 using 3.3 g of the iodinated derivative prepared in Stage A, 1.5 cm<sup>3</sup> of thieno-[3,2-b]-pyridine and replacing the dimethylsulphoxide with methylene chloride. 1.08 g of expected product is obtained.

20 NMR

-CH=CH-CH<sub>2</sub>-N<sup>+</sup> : 5.69 to 5.84 (m) 3H (+ H<sub>7</sub>)

-CH=CH-CH<sub>2</sub>-N<sup>+</sup> : 6.33 (dt), 6.46 (dt)

H of thienopyridine : 7.83 to 9.72

STAGE C: [6R-[3(E) 6alpha, 7beta(Z)]]-4-[3-[[[(2-amino-4-thiazolyl)-[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2(E)-propenyl]-thieno-[3,2-b]-pyridinium trifluoroacetate tetrafluoroacetate.

The following two solutions are mixed together at 0°C and agitated for one hour:

a) 55 cm<sup>3</sup> of trifluoroacetic acid, 5.5 cm<sup>3</sup> of anisole and 25 cm<sup>3</sup> of methylene chloride,

b) 1.19 g of the product obtained as in Stage B in 20 cm<sup>3</sup> of methylene chloride and the synthesis is continued as indicated

in Stage C of Example 3. 0.62 g of expected product is obtained.

NMR (DMSO 400 Hz)



$\text{=N-O-CH-CO}_2\text{H}$  : 5.33 (s)  
 $\text{-CH-S}$  : 5.15 (d, resolved)

N

5  $\text{S-CH}_2\text{-}$  : 3.49 (m) partially masked  
 $\text{-CH=CH-CH}_2$  : 6.33 (dt, J=16 and 8) delta E  
 $\text{-H=CH-CH}_2$  : 5.72 (m)  
 and  
 $\text{-CH=CH-CH}_2$

10

phenyl  
 $\text{H}_5$  thiazole : 6.57 to 7.01

mobile H

H of thienopyridine : 8.04 to 9.36

15 **EXAMPLE 7:** [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-pyridinium trifluoroacetate hydroiodide.

20 **STAGE A:** [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[1-[3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(diphenylmethoxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl] pyridinium

25 iodide.

The operation is carried out as in Stage B of Example 6 starting with 1.47 g of the iodinated derivative obtained as indicated in Stage A of Example 3 and 480 microlitres of pyridine. 0.640 g of expected product is obtained.

30 NMR ( $\text{CDCl}_3$  400 MHz)

$\text{-CH=CH-CH}_2\text{-N}^{\oplus}$  : 5.15 to 5.50  
 $\text{-CH=CH-CH}_2\text{-N}^{\oplus}$  : 6.5 (dt, resolved) delta E  
 $\text{H}_2$  and  $\text{H}_6$  of pyridine : 9.10 (m)  
 $\text{H}_3$  and  $\text{H}_5$  of pyridine : 7.87 (m)  
 35  $\text{H}_4$  of pyridine : 8.27 (t, resolved)

**STAGE B:** [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-

[4,2,0]-oct-2-en-3-yl]-2-propenyl]-pyridinium trifluoroacetate hydroiodide.

The operation is carried out as in Stage C of Example 6 using 0.638 g of the derivative obtained in the preceding 5 Stage and 0.314 g of expected product is obtained.

NMR

$\text{=N-O-CH-CO}_2\text{H}$  : 5.32 (s)  
 $\text{H}_6$  : 5.14 (d) and 5.17 (d)  
 10  $\text{H}_7$  : 5.77 (m)  
 $\text{H}_5$  thiazole : 6.87 (sl)  
 $\text{C-NH-CH}$  : 9.55 (d) and 9.62 (d)  
 phenyl : 6.65 to 6.80  
 $-\text{CH=CH-CH}_2$  : 7.01 (d, resolved)  
 15  $-\text{CH=CH-CH}_2$  : 6.30 (dt) delta E  
 $-\text{CH=CH-CH}_2$  approx. 5.41  
 H in position 2 and 6 of pyridine : 9.05 (d)  
 H in position 3 and 5 of pyridine approx. 8.13 (d)  
 H in position 4 of pyridine : 8.64 (t)

20 **EXAMPLE 8:** [6R-[3(E), 6alpha, 7beta(Z)]]-6-[3-[7-[[2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-

[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-c]-pyridinium trifluoroacetate hydroiodide.  
 25 **STAGE A:** [6R-[3(E), 6alpha, 7beta(Z)]]-6-[3-[7-[[[1-[3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(diphenylmethoxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-c]-  
 30 pyridinium iodide.

The operation is carried out as in Stage B of Example 6 starting with 2.08 g of the iodinated derivative prepared as indicated in Stage A of Example 3 and 1 g of thieno-[2,3-c] pyridine. 0.98 g of expected product is obtained.

35 NMR

1) In EtOH:

Infl.	220 nm	epsilon = 87500
max.	239 nm	epsilon = 57000
Infl.	274 nm	epsilon = 25500

max. 306 nm epsilon = 27000

1) In EtOH/HCl 0.1N:

Infl. 220 nm epsilon = 87800

Infl. 236 nm epsilon = 53600

5 max. 284 nm epsilon = 32600

max. 293 nm epsilon = 32500

Infl. 320 nm epsilon = 24000

STAGE B: 6R-[3(E), 6alpha, 7beta(Z)]-6-[3-[7-[(2-amino-4-thiazolyl)-[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-c]-pyridinium trifluoroacetate hydroiodide.

The operation is carried out as in Stage C of Example 6 using 0.966 g of the iodinated derivative obtained in the preceding Stage A and 0.487 g of expected product is obtained.  
NMR

$\text{=N-O-CH-CO}_2\text{H}$  : 5.32 (s)

H<sub>7</sub> : 5.78 (m)

20 H<sub>5</sub> thiazole : 6.86 (sl)

phenyl : 6.65 to 6.80

H<sub>6</sub>, H<sub>7</sub> thienopyridine : 7.94 (d), 8.81 (d)

H<sub>4</sub>, H<sub>5</sub> thienopyridine : 8.53 (d), 8.78 (d)

H<sub>2</sub> thienopyridine : 9.91 (s)

25  $\text{-CH=CH-CH}_2$  : 7.08 (dl, J=15.5)

$\text{-CH=CH-CH}_2$  : 6.35 (m) delta E

$\text{-CH-CH-CH}_2$  : 5.47 (d)

EXAMPLE 9: [6R-[3(E), 6alpha, 7beta(Z)]-1-[3-[7-[(2-amino-4-thiazolyl)-[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-6,7-dihydro-5H-pyridinium trifluoroacetate iodide.

STAGE A: [6R-[3(E), 6alpha, 7beta(Z)]-5-[3-[7-[[1-[3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(diphenylmethoxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-6,7-dihydro-5H-pyridinium iodide





The operation is carried out as in Stage B of Example 6 starting with 1.33 g of the iodinated derivative prepared as in Stage A of Example 3 and 0.585 cm<sup>3</sup> of cyclopentyl pyridine. 1.07 g of expected product is obtained.

5 **STAGE B:** [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-6,7-dihydro-5H-pyridinium trifluoroacetate iodide.

10 The operation is carried out as in Stage C of Example 6 using 1.053 g of the product obtained in stage A and the expected product is obtained.

NMR (DMSO 300 MHz)

15	CH <sub>2</sub> -N <sup>+</sup>	5.32 (m) 3H
	O-CH- $\gamma$	
	Aromatic H's	
	H <sub>5</sub> thiazole	6.70 to 6.90
	-CH-CH-CH <sub>2</sub>	
20	H <sub>6</sub>	: 5.16 (d, resolved)
	H <sub>7</sub>	: 5.77 (m, d, resolved after exchange)
	-S-CH <sub>2</sub>	: 3.4 to 3.8(m)
	-CH=CH-CH <sub>2</sub>	: 6.23 (d, t) delta E
	H of cyclopentyl	: 2.23-3.15-3.8
25	H of pyridine	: 7.2 (m), 8.42 (d), 8.76 (d)
	Mobile H	: 9.01 to 9.62
	-CH-CH-CH <sub>2</sub>	: 5.47 (d)

**EXAMPLE 10:** [6R-[3(E), 6alpha, 7beta(Z)]]-2-amino-5-[3-[7-[[2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thiazolo-[4,5-c]-pyridinium trifluoroacetate iodide

**STAGE A:** [6R-[3(E), 6alpha, 7beta(Z)]]-2-amino-5-[3-[7-[[1-[3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxoethoxy]-imino]-2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(diphenylmethoxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thiazolo-[4,5-c] pyridinium iodide.



The operation is carried out as in Stage B of Example 6 starting with the iodinated derivative prepared as in Stage A of Example 3 (from 272 mg of the chlorinated derivative and 90 mg of sodium iodide) and 30 mg of amino thiazolo pyridine. 42 5 mg of expected product is obtained.

**STAGE B:** [6R-[3(E), 6alpha, 7beta(Z)]]-2-amino-5-[3-[7-[[2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-aza-bicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thiazolo-[4,5-c]-10 pyridinium trifluoroacetate iodide.

The operation is carried out as in Stage C of Example 3 using 130 mg of the product obtained as in Stage A and 11.5 mg of expected product is obtained.

NMR (DMSO 400 MHz)

15	H <sub>5</sub> thiazole ethylenic aromatics	6.64 to 7.41
20	N <sup>6</sup> -CH <sub>2</sub> -CH- O-CH-	5.05 to 5.35
	H <sub>7</sub>	: 5.67 (m), 5.76 (m)
	-CH=CH-CH <sub>2</sub> -	: 6.29
	H <sub>6</sub> , H <sub>7</sub> of thiazolo pyridine	: 8.42 (d), 8.49 (d)
25	H <sub>2</sub> of thiazolo pyridine	: 8.99 (sl)
		8.67
	mobile protons	9 (m)
		9.54 (m)
30		10.15

**EXAMPLE 11:** [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[3,2-c]-35 pyridinium trifluoroacetate hydroiodide.

**STAGE A:** [6R-[3(E), 6alpha, 7beta(Z)]]-p-methoxybenzyl-7-[[[1-[3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-(diphenyl-methoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-

thiazolyl]-acetyl]-amino]-3-(3-chloro-1-propenyl)-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl-2-carboxylate.

A suspension containing 3.75 g of [(3,4-bis[(2-methoxyethoxy)-methoxy]-phenyl)-2-(diphenylmethoxy)-2-oxoethoxy]-5 imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetic acid syn isomer, described in the European Patent EP 238061 and 1.81 g of methoxybenzyl-7-amino-3-(3-chloropropenyl)-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-2-carboxylate (prepared as indicated in the European Patent EP 0,333,154 in methylene

10 chloride is cooled down to 0°C, and 0.920 g of N-(dimethylaminopropyl)-N'-ethyl carbodiimide hydrochloride is added. The solution obtained is kept under agitation at 0°C for 30 minutes. The organic phase is washed with an aqueous solution of sodium chloride, dried and the solvents are

15 eliminated. After chromatographing the residue on silica (eluant: methylene chloride - ether 85-15) and solidification in isopropyl ether, 4.546 g of expected product is obtained.

NMR (CDCl<sub>3</sub> 400 MHz)

CO<sub>2</sub>-CH<sub>2</sub>-Y : 5.10 to 5.32

20 Y-O-CH<sub>3</sub> : 3.80

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-p-methoxybenzyl-7-[[[1-[3,4-bis[(2-methoxyethoxy)-methoxy]-phenyl)-2-(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-3-(3-iodo-1-propenyl)-8-oxo-5-thia-

25 1-azabicyclo-[4,2,0]-oct-2-en-3-yl-2-carboxylate.

A mixture of the product obtained in stage A, 10 cm<sup>3</sup> of acetone and 341 mg of sodium iodide and approximately 10 mg of iodine is agitated for one hour at ambient temperature, the solvent is evaporated off then the residue is taken up in 80

30 cm<sup>3</sup> of methylene chloride. The organic phase is washed with an aqueous solution of sodium thiosulfate then with water. After drying, the solvents are eliminated and the residue is chromatographed on silica (eluant: methylene chloride - ethyl acetate 8-2) and 853 mg of expected product is obtained.

35 NMR (CDCl<sub>3</sub> 300MHz)

-CH=CH-CH<sub>2</sub>

aromatics

CH=C

6.9 to 7.35

-CH=CH-CH<sub>2</sub> : 6.13 (d, t J=15 and 8) delta E

-CH=CH-CH<sub>2</sub> : 4.0 (d)

**STAGE C:** [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[[1-[3,4-  
5 bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-  
2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-  
acetyl]-amino]-2-[(paramethoxy-benzyloxy)-carbonyl]-8-oxo-5-  
thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-  
[3,2-c] pyridinium iodide.

10 2.48 g of the iodinated derivative is dissolved in 10 cm<sup>3</sup>  
of methylene chloride and 1.2 g of thieno-[3,2-c] pyridine in  
solution in 2 cm<sup>3</sup> of methylene chloride is added and  
trituration takes place for 1 hour at ambient temperature. 70  
cm<sup>3</sup> of ether is added, the precipitate is filtered, washed  
15 with ether and chromatographed on silica (eluant: methylene  
chloride - methanol 95-5) and 1.117 g of expected product is  
obtained.

**STAGE D:** [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[2-amino-4-  
thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-  
20 imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-  
[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[3,2-c]-pyridinium  
trifluoroacetate hydroiodide.

The operation is carried out as in Stage C of Example 6  
using 1.117 g of the product obtained in Stage C and 0.618 g  
25 of expected product is obtained.

NMR (DMSO 300 MHz)

30 =N-O-CH-CO<sub>2</sub>H : 5.33 (s)  
H<sub>6</sub> : 5.18  
H<sub>7</sub> : 5.79 (m)  
N-NH-CH : 9.56 (d), 9.64 (d)  
-CH=CH-CH<sub>2</sub> : 7.07 (d, J=15.5) delta E  
-CH=CH-CH<sub>2</sub> : 6.36 (m)  
H of thienopyridine : 8 to 9.71  
35 aromatics and H<sub>5</sub> thiazole : 6.70 to 6.78; 6.85 (s,1)  
mobile H's : 12.56

**EXAMPLE 12:** [6R-[(E), 6alpha, 7beta(Z)]]-2-[3-[7-[[2-amino-4-  
thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-

imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-isoquinolinium trifluoroacetate hydroiodide.

STAGE A: [6R-[3(E), 6alpha, 7beta(Z)]]-2-[3-[7-[[[1-[3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxoethoxy]-imino]-2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(paramethoxybenzyl)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-isoquinolinium iodide.

10 The operation is carried out as in Stage B of Example 6 starting with 2.48 g of iodinated derivative prepared as in Stage B of Example 11 and 1.04 cm<sup>3</sup> of isoquinoline. 1.26 g of expected product is obtained.

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-2-[3-[7-[[[2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-isoquinolinium trifluoroacetate hydroiodide.

20 The operation is carried out as in Stage C of Example 6 using 1.26 g of the product obtained in Stage A and 0.673 g of expected product is obtained.

NMR (DMSO 300 MHz)

	$\text{=N-O}-\overset{\text{Y}}{\text{CH}}-\text{CO}_2\text{H}$	: 5.32 (s)
25	H <sub>6</sub>	: 5.17 (m)
	H <sub>7</sub>	: 5.77 (m)
	S -CH <sub>2</sub>	: 3.07
	N-NH-CH	: 9.54 (d), 9.62 (d)
	-CH=CH-CH <sub>2</sub>	: 7.10 delta E
30	-CH=CH-CH <sub>2</sub>	: 6.37 (m) delta E
	-CH=CH-CH <sub>2</sub> -	: 5.53 (d)
	H of isoquinoline	: 8.9 to 10.06
	aromatics and H <sub>5</sub> thiazole	: 6.45 to 6.37 (3H); 6.85 (s) H
	mobile H's	: 7.30 (2H); 9 (2H)

35 EXAMPLE 13: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[[2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-2-methyl-1H-

imidazo-[4,5-c]-pyridinium trifluoroacetate hydroiodide.













**STAGE A:** [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[[1-[3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxoethoxy]-imino]-2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(paramethoxybenzyl)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-2-methyl-1H-imidazo-[4,5-c]-pyridinium iodide.

The operation is carried out as in Stage B of Example 6 starting with 1.92 g of the iodinated derivative prepared as in Stage B of Example 11 and 0.29 g of 2-methyl-1H-imidazo-[4,5-c]-pyridine. 1.055 g of expected product is obtained.

**STAGE B:** [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-2-methyl-1H-imidazo-[4,5-c]-pyridinium trifluoroacetate hydroiodide.

The operation is carried out as in Stage C of Example 6 using 1.043 g of the product obtained in Stage A and 0.608 g of expected product is obtained.

20 NMR (DMSO 300 MHz)

	=N-O- <u>CH</u> -CO <sub>2</sub> H	: 5.32 (s)
	H <sub>6</sub>	: 5.15 (d, resolved)
	H <sub>7</sub>	: 5.77 (m, d, resolved after exchange)
	25 S- <u>CH</u> <sub>2</sub>	: 3.76 (d), 3.61 (masked)
	N- <u>NH</u> -CH	: 9.55 (d), 9.63 (d)
	- <u>CH</u> =CH-CH <sub>2</sub>	: 6.95 (dl)
	-CH= <u>CH</u> -CH <sub>2</sub>	: 6.35 (dt) delta E
	-CH=CH- <u>CH</u> <sub>2</sub> -	: 5.42 (m)
	30 CH <sub>3</sub> of imidazopyridine:	2.70 (s)
	H of pyridine	: 8.16 to 9.47
	aromatics and H <sub>5</sub> thiazole	: 6.65 to 6.80 (m) 3H; 6.86 (s) 1H
	mobile H's	: 7.34 (2H); 9.05 (m)

**EXAMPLE 14:** [6R-[3(E), 6alpha, 7beta(Z)]]-3-[7-[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N,N,N-trimethyl-2-propen-1-aminium trifluoroacetate iodide

**STAGE A:** [6R-[3(E), 6alpha, 7beta(Z)]]-3-[7-[[[1-[3,4-bis[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxo-ethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(paramethoxybenzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N,N,N-trimethyl-2-propen-1-aminium iodide.

365 mg of the iodinated derivative as in Stage B of Example 11, 0.7 cm<sup>3</sup> of tetrahydrofuran and 220 microlitres of a solution of trimethylamine in ether (2.37 M/l) are agitated for 40 minutes at ambient temperature. 20 cm<sup>3</sup> of ether is added, the precipitate is separated and chromatographed on silica (eluant: methylene chloride - methanol 92-8), the residue is taken up in ether and after elimination of the solvent 276 mg of expected product is obtained.

15 Infra-Red

=C-NH

3404 cm<sup>-1</sup> + associated

>O

20

1791 cm<sup>-1</sup> (beta lactame)

1728 cm<sup>-1</sup> esters

1685 cm<sup>-1</sup> amide

Conjugated system

25 + amide II

+ aromatic

1632 cm<sup>-1</sup> (shoulder)

1613 cm<sup>-1</sup>

1596 cm<sup>-1</sup>

1586 cm<sup>-1</sup>

1525 cm<sup>-1</sup>

1517 cm<sup>-1</sup>

1496 cm<sup>-1</sup>

Ultra-violet

30 1) In ethanol + 1 cm<sup>3</sup> CH<sub>2</sub>Cl<sub>2</sub>

infl. 219 nm epsilon = 74000

max. 281 nm epsilon = 23600

infl. 295 nm epsilon = 22100

infl. 265, 276 nm

35 2) In ethanol HCl 0.1n

infl. 219 nm epsilon = 75000

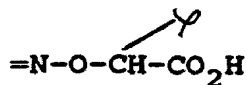
max. 283 nm epsilon = 30000

**STAGE B:** [6R-[3(E), 6alpha, 7beta(Z)]]-3-[7-[[[2-amino-4-

thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N,N,N-trimethyl-2-propen-1-aminium trifluoroacetate iodide.

- 5 247 mg of product obtained in Stage A with 2.5 cm<sup>3</sup> of trifluoroacetic acid with 10% of anisole is agitated for 1 hour at ambient temperature. 25 cm<sup>3</sup> of isopropyl ether is added, agitation is carried out for 10 minutes, the precipitate formed is isolated and dried under reduced  
10 pressure at 20°C for 24 hours. 128 mg of expected product is obtained.

NMR (DMSO 300 MHz)

		: 5.33 (s)
15	H <sub>6</sub>	: 5.16 (d)
	H <sub>7</sub>	: 5.76 (d)
	N-NH-CH	: 9.08 (d)
	-CH=CH-CH <sub>2</sub>	: 6.07 (m) delta E
	-CH=CH-CH <sub>2</sub>	: 7.04 (d)
20	-CH=CH-CH <sub>2</sub> -	: 4.05 (d)
	+ N-(CH <sub>3</sub> ) <sub>3</sub>	: 2.99 (s), 3.03 (s)
	aromatics and H <sub>5</sub> thiazole	: 6.70 to 6.9

**EXAMPLE 15:** [6R-[3(E), 6alpha, 7beta(Z)]]-[3-[7- [(2-amino-4 thiazolyl)-[[1-(3,4-dihydroxy phenyl)-2- hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N- (cyanomethyl)-N,N-dimethyl-2-propen-1-aminium] trifluoro-acetate iodide.

- STAGE A:** [6R-[3(E), 6alpha, 7beta(Z)]]-[3-[7-[[[1-[3,4-bis-[(2-methoxy ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(paramethoxybenzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N-(cyanomethyl)-N,N-dimethyl-2-propen-1-aminium] iodide.

- The operation is carried out as in Stage A of Example 14  
35 starting with 250 mg of the iodinated derivative and 250 cm<sup>3</sup> of a solution of dimethylamino acetonitrile in tetrahydrofuran (1-9). 172 mg of expected product is obtained.

NMR (CDCl<sub>3</sub> 400 MHz)



-CH=CH-CH<sub>2</sub>: 6.05 (d,t) delta E

-CH=CH-CH<sub>2</sub>- 5.05 to 5.35

CO<sub>2</sub>-CH<sub>2</sub>-

+ N-CH<sub>2</sub>-CN: 4.35 to 4.5

5 the CH<sub>3</sub>'s : 3.07 to 3.9

**STAGE B:** [6R-[3(E), 6alpha, 7beta(Z)]]-[3-[7-[[2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N-(cyanomethyl)-N,N-dimethyl-2-propen-1-aminium]-trifluoroacetate iodide.

The operation is carried out as in Stage B of Example 14 starting with 172 mg of product prepared in Stage A. 72 mg of expected product is obtained.

NMR (DMSO 300 MHz)

15

=N-O-CH-CO<sub>2</sub>H : 5.33 (s)

H<sub>6</sub> : 5.20 (d)

H<sub>7</sub> : 5.82 (m)

N-NH-CH : 9.54 (d)

20 -CH=CH-CH<sub>2</sub> : 7.1 (d)

-CH=CH-CH<sub>2</sub> : 6.13 (m)

-CH=CH-CH<sub>2</sub>- : 4.24 (d)

⊕ N-(CH<sub>3</sub>)<sub>2</sub> : 3.19 (s)

⊕ N-CH<sub>2</sub>-CN : 4.8 (s)

25 aromatics and H<sub>5</sub> thiazole : 6.65 to 6.80 and 6.87

mobile H's : 7.79; 9.07

**EXAMPLE 16:** [6R-[3(E), 6alpha, 7beta(Z)]]-N-(2-amino-2-oxoethyl)-[3-[7-[[2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N,N-dimethyl-2-propen-1-aminium]-trifluoroacetate iodide.

**STAGE A:** [6R-[3(E), 6alpha, 7beta(Z)]]-N-(2-amino-2-oxoethyl)-[3-[7-[[1-[3,4-bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(paramethoxybenzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N,N-dimethyl-2-propen-1-aminium] iodide.

350 mg of the iodinated derivative obtained as indicated in Stage B of Example 11 is mixed over one hour at 20°C with 1.6 cm<sup>3</sup> of acetonitrile and 27 mg of dimethylaminoacetamide. The solvents are eliminated under reduced pressure, the residue is chromatographed on silica (eluant: methylene chloride - methanol 97-3 then 92-8). 300 mg of expected product is collected.

NMR (CDCl<sub>3</sub> 300 MHz)

-CH=CH-CH<sub>2</sub>- : 6.10 delta E

10 -CH=CH-CH<sub>2</sub>- : 4.56

-CH=CH-CH<sub>2</sub>

aromatic H's 6.85 to 7.37

NH<sub>2</sub>

the CH<sub>3</sub>'s : 3.24 to 3.35

15 <sup>⊕</sup>N-CH<sub>2</sub>-C : 4.23 (m)

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]-N-(2-amino-2-oxoethyl)-[3-[7-[[2-amino-4-thiazolyl)-[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-N,N-dimethyl-2-

20 propen-1-aminium] trifluoroacetate iodide.

The operation is carried out as in Stage B of Example 14 starting with 285 mg of product prepared as in Stage A above. 152 mg of expected product is obtained.

NMR (DMSO 300 MHz)

25 =N-O-CH-CO<sub>2</sub>H : 5.34 (s)

H<sub>6</sub> : 5.19 (d)

H<sub>7</sub> : 5.85 (m)

the NH's : 9.55 (d); 9.62 (d)

30 -CH=CH-CH<sub>2</sub> : 7.03 (d, J=13.5) delta E

-CH=CH-CH<sub>2</sub> : 6.13 (m)

-CH=CH-CH<sub>2</sub>- : 4.27 (d)

<sup>⊕</sup>N-(CH<sub>3</sub>)<sub>2</sub> : 3.19 (s)

<sup>⊕</sup>N-CH<sub>2</sub>- : 4.01 (s)

35 aromatics and H<sub>5</sub> thiazole : 6.72 to 6.8

mobile H's

EXAMPLE 17: [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[2-amino-4-thiazolyl)-[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-

oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-1-methyl-pyrrolidinium trifluoroacetate iodide.

STAGE A: [6R-[3(E), 6alpha,7beta(Z)]]-[3-[7-[[[1-[3,4-bis-(2-methoxy ethoxy)-methoxy]-phenyl]-2-[(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(paramethoxybenzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-1-methyl pyrrolidinium iodide.

10 357 mg of iodinated derivative obtained as indicated in Stage B of Example 11 is dissolved at 20°C in 7 cm<sup>3</sup> of ether and 1.3 cm<sup>3</sup> of methylene chloride. 130 microlitres of methylpyrrolidine and 5 cm<sup>3</sup> of ether are added, agitation is carried out for 10 minutes, the precipitate is isolated and dried at 15 20°C under reduced pressure. 300 mg of expected product is obtained.

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-20 [4,2,0]-oct-2-en-3-yl]-2-propenyl]-1-methyl pyrrolidinium trifluoroacetate iodide.

The operation is carried out as in Stage B of Example 14 starting with 290 mg of product obtained in Stage A above. 150 mg of expected product is obtained.

25 NMR (DMSO 300 MHz)

	=N-O- <sup>γ</sup> CH-CO <sub>2</sub> H	: 5.34 (s)
	H <sub>6</sub>	: 5.18 (d)
30	H <sub>7</sub>	: 5.79 (m)
	the -NH-CH's	: 9.52 (d); 9.61 (d)
	-CH=CH-CH <sub>2</sub>	: 7.05 (d, J=15) delta E
	-CH=CH-CH <sub>2</sub>	: 6.17 (m) delta E
	-CH=CH-CH <sub>2</sub> -	: 4.11 (d)
35	⊕ N-CH <sub>3</sub>	: 2.99 (s)
	pyrrolidine	: 2.10 (sl), 3.45 (sl)
	aromatics and H <sub>5</sub> thiazole	: 6.65 to 6.85
	mobile H's	: 9.10

**EXAMPLE 18:** [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[2-amino-4-thiazolyl)-[(R) 1-(3,4-dihydroxy phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b]-5 pyridinium trifluoroacetate hydroiodide.

**STAGE A:** [6R-[3(E), 6alpha, 7beta(Z)]]-p-methoxybenzyl-7-[[[(R)-1-[3,4-dihydroxy)-phenyl]-2-(diphenylmethoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-3(3-chloro-1-propenyl)-8-oxo-5-thia-1-10 azabicyclo-[4,2,0]-oct-2-en-3-yl-2-carboxylate.

1.1 g of [[(R) (3,4-dihydroxyphenyl)-(diphenylmethoxy-carbonyl)-methoxy]-imino]-[2-(triphenylmethylamino)-4-thiazolyl] acetic acid syn isomer (prepared as indicated for isomer S in the European Patents EP 0,266,060 and 0,280,521 or 15 in the German Patent DE 37 42 457 A1) in 11.36 cm<sup>3</sup> of methylene chloride. The solution obtained is cooled to -5°C, 403.4 mg of dicyclocarbodiimide is added, agitation is carried out for 40 minutes and 668 mg of p-methoxybenzyl-7-amino-3-(3-chloro-1-propenyl)-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-20 2-carboxylate hydrochloride prepared as indicated in the European Patent EP 0,333,154. Agitation is carried out for 3 hours while allowing the temperature to return to ambient, the solvents are eliminated, the residue is chromatographed on silica (eluant: methylene chloride - ethyl acetate 9-1) and 25 712 mg of expected product is obtained.

NMR (CDCl<sub>3</sub> 300 MHz)

aromatics

30	COO-CH- $\varphi_2$	6.74 to 7.34
	thiazole	
	=C-CH=CH	
	-CH=CH-CH <sub>2</sub>	: 6.25 (d, J=1) delta Z
35	-CH=CH-CH <sub>2</sub>	3.73 (dd)
		3.92 (dd)
	CO <sub>2</sub> -CH <sub>2</sub> -	5.18 (s)
		5.24

-OCH<sub>3</sub> : 3.81 (s)

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-p-methoxybenzyl-7-  
[[[(R)-1-[3,4-[(dihydroxy)-phenyl]-2-(diphenylmethoxy)-2-  
5 oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-  
acetyl]-amino]-3(3-iodo-1-propenyl)-8-oxo-5-thia-1-azabicyclo-  
[4,2,0]-oct-2-en-3-yl-2-carboxylate.

A mixture of 590 mg of product obtained in Stage A, 11.9  
cm<sup>3</sup> of acetone and 216 mg of sodium iodide is agitated for 2  
10 hours at ambient temperature, the solvent is evaporated then  
the residue is taken up in 5 cm<sup>3</sup> of methylene chloride. The  
solution is washed with 3 times 10 cm<sup>3</sup> of sodium thiosulphate  
then with 2 times 10 cm<sup>3</sup> of an aqueous solution of sodium  
chloride. After drying and crystallizing from ether, 456.6 mg  
15 of expected product is obtained.

NMR (CDCl<sub>3</sub> 400 MHz)

=N-O-CH-CO<sub>2</sub>H : 5.86 (s)  
H<sub>6</sub> : 4.85 (d)  
20 H<sub>7</sub> : 5.74 (dd)  
S-CH<sub>2</sub> : 3.24  
C-NH-CH : 8.10 (d)  
-CH=CH-CH<sub>2</sub> : 6.00 (d, J=15.5 and 17.5) delta E  
-CH=CH-CH<sub>2</sub>- : 3.82 (d), 3.98 (d)  
25 -CO<sub>2</sub>-CH<sub>2</sub>- : 5.24  
γ-O-CH<sub>3</sub> : 3.80 (s)  
aromatics and H<sub>5</sub> thiazole : 6.68 to 7.40

STAGE C: [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[[(R)-1-[3,4-  
bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenyl-  
30 methoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-  
thiazolyl]-acetyl]-amino]-2-[(p-methoxybenzyloxy)-carbonyl]-8-  
oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-  
thieno-[2,3-b] pyridinium iodide.

446 mg of iodinated derivative obtained in Stage B and  
35 0.44 cm<sup>3</sup> of thieno pyridine are agitated and triturated for 2  
hours at ambient temperature. Ether is added and the solid  
obtained is dried under reduced pressure for 24 hours. 442 mg  
of expected product is obtained.

NMR

$\text{=N-O-CH-}$   $\gamma$  : 5.55  
 $\text{-CH=CH-CH}_2$  : 6.30 (m) delta E

5  $\text{-CH=CH-CH}_2$  : 5.63 to 5.69  
 $\text{H}_7$

H of the thieno pyridine : 7.89 to 9.21

**STAGE D:** [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[2-amino-4-thiazolyl]-[(R)-1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxo-ethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b]-pyridinium trifluoroacetate hydroiodide.

632 mg of product obtained as in Stage C in 6.32 cm<sup>3</sup> of a solution of trifluoroacetic acid with 10% anisole is agitated for one hour at ambient temperature. The mixture is cooled to +5°C, 65 cm<sup>3</sup> of isopropyl ether is added, followed by agitating for 10 minutes, filtering and drying under reduced pressure at ambient temperature for 16 hours. 403 mg of expected product is obtained.

NMR (DMSO 400 MHz)

$\text{=N-O-CH-CO}_2\text{H}$   $\gamma$  : 5.31 (s)  
 $\text{H}_6$  : 5.18 (d)  
 25  $\text{H}_7$  : 5.77 (dd)  
 $\text{S-CH}_2$  : 3.73 (m)  
 $\text{-CH-CH-CH}_2$  : 7.15 (d, J=16) delta E  
 $\text{-CH=CH-CH}_2$  : 6.30 (d,t)

30  $\text{-CH=CH-CH}_2\text{-}$  : 5.68 (d)  
 H of the thieno pyridine : 7.88 to 9.23  
 aromatics, NH, H<sub>5</sub> thiazole : 6.70 to 7.35 (approx. 6H)  
 mobile H's : 7.31 to 9.61

**EXAMPLE 19:** [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[2-amino-4-thiazolyl]-[(S)-1-(3,4-dihydroxy phenyl)-2-hydroxy-2-oxo-ethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b]-pyridinium trifluoroacetate iodide.

**STAGE A:** [6R-[3(E), 6alpha, 7beta(Z)]]-p-methoxybenzyl-7-  
 [[[(S)-1-[3,4-dihydroxy)-phenyl]-2-(diphenylmethoxy)-2-  
 oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-  
 acetyl]-amino]-3-(3-chloro-1-propenyl)-8-oxo-5-thia-1-  
 5 azabicyclo-[4,2,0]-oct-2-en-3-yl-2-carboxylate.

The operation is carried out as in Stage A of Example 18  
 starting with 678 mg of [[(S) (3,4-dihydroxyphenyl)-  
 (diphenylmethoxycarbonyl)-methoxy]-imino]-[2-(triphenyl-  
 methylamino)-4-thiazolyl] acetic acid syn isomer prepared as  
 10 indicated in the European Patents EP 0,266,060 and 0,280,521  
 or in the German Patent DE 37 32 457 A1 and 412 mg of p-  
 methoxybenzyl hydrochloride of 7-amino-3-(3-chloro-1-  
 propenyl)-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-2-  
 carboxylate. 590 mg of expected product is obtained.

15 NMR (CDCl<sub>3</sub> 400 MHz)

=N-O-CH-	:	5.89 (s)
-CH=CH-CH <sub>2</sub>		5.81 (d,t)
		6.34 (d, J=12)

**STAGE B:** [6R-[3(E), 6alpha, 7beta(Z)]]-p-methoxybenzyl-7-  
 20 [[[(S)-1-[3,4-[(dihydroxy)-phenyl]-2-(diphenylmethoxy)-2-  
 oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-  
 acetyl]-amino]-3-(3-iodo-1-propenyl)-8-oxo-5-thia-1-  
 azabicyclo-[4,2,0]-oct-2-en-3-yl-2-carboxylate.

The operation is carried out as in Stage B of Example 18  
 25 using 850 mg of the product obtained in Stage A and 335 mg of  
 sodium iodide. 595 mg of expected product is obtained.

Infra Red (CHCl<sub>3</sub>)

30		3548 cm <sup>-1</sup>
	OH	3478 cm <sup>-1</sup>
	NH	3401 cm <sup>-1</sup>
		3284 cm <sup>-1</sup>
		1772 cm <sup>-1</sup> beta lactame
35	>C=O	1725 cm <sup>-1</sup> ester
		1684 cm <sup>-1</sup> amide

	1614 $\text{cm}^{-1}$
aromatic	1601 $\text{cm}^{-1}$
heterocycle	1586 $\text{cm}^{-1}$
amide II	1529 $\text{cm}^{-1}$
5 C=C	1517 $\text{cm}^{-1}$
	1496 $\text{cm}^{-1}$

## Ultra Violet

## 1) in dioxane:

	infl. 224 nm	$E_1^1 = 566$	epsilon = 69600
10	infl. 242 nm	$E_1^1 = 345$	
	infl. 275 nm	$E_1^1 = 197$	
	max. 282 nm	$E_1^1 = 201$	epsilon = 24700
	infl. 290 nm	$E_1^1 = 195$	
	max. 314 nm	$E_1^1 = 218$	epsilon = 26800

## 15 2) in dioxane/HCl 0.1N

	max. 285 nm	$E_1^1 = 266$	epsilon = 32700
	infl. 304 nm	$E_1^1 = 244$	epsilon = 30000
	infl. 320 nm	$E_1^1 = 188$	epsilon = 23100

20 STAGE C: [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[[(S)-1-[3,4-bis-[(2-methoxy ethoxy)-methoxy]-phenyl]-2-[(diphenyl-methoxy)-2-oxoethoxy]-imino] [2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(p-methoxybenzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b]-pyridinium iodide.

25 The operation is carried out as in Stage C of Example 18 using 430 mg of iodinated derivative obtained in Stage B and 470 mg of thieno pyridine. 438 mg of expected product is obtained.

30 Infra Red ( $\text{CHCl}_3$ )

## NH/OH region complex

	1780 $\text{cm}^{-1}$	beta lactame
35 -C=O	1725 $\text{cm}^{-1}$	ester
	1684 $\text{cm}^{-1}$	amide



	1613 cm <sup>-1</sup>
	1600 cm <sup>-1</sup>
aromatic	1586 cm <sup>-1</sup>
heterocycle	1575 cm <sup>-1</sup>
5 Amide II	1558 cm <sup>-1</sup>
+ >C=C<	1525 cm <sup>-1</sup>
	1516 cm <sup>-1</sup>
	1496 cm <sup>-1</sup>

**STAGE D:** [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[2-amino-4-thiazolyl)-[(S)-1-(3,4-dihydroxy phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b]pyridinium trifluoroacetate iodide.

The operation is carried out as in Stage D of Example 18 using 400 mg of product obtained in Stage C. 275 mg of expected product is obtained.

NMR (DMSO 400 MHz)

	$\text{=N-O-CH-CO}_2\text{H}$	: 5.32 (s)
20	H <sub>6</sub>	: 5.15
	H <sub>7</sub>	: 5.80 (dd, sl after exchange)
	CO-NH-	: 9.55 (d)
	C-NH-CH	: 9.55 (d)
	S-CH <sub>2</sub>	: 3.51 (m)
25	-CH-CH-CH <sub>2</sub>	: 7.13 (d, J=16) delta E
	-CH=CH-CH <sub>2</sub>	: 6.27 (d,t J=16 and 6)
	-CH=CH-CH <sub>2</sub> -	: 5.67 (d, J=6)

H of the thieno pyridine : 7.89 to 9.55

aromatics and H<sub>5</sub> thiazole : 6.60 to 6.87 (m)

**EXAMPLE 20:** [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-1,2-dimethylimidazo-[4,5-c] pyridinium trifluoroacetate hydroiodide.

**STAGE A:** [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[[1-[3,4-bis-[(2-methoxy ethoxy)-methoxy]-phenyl]-2-[(diphenyl-methoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-

acetyl]-amino]-2-[(paramethoxybenzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-1,2-dimethylimidazo-[4,5-c]-pyridinium iodide.

1.08 g of product obtained as indicated in Stage B of Example 11 is agitated for one hour with 170 mg of 1,2-dimethyl-4-aza benzimidazole in 0.9 cm<sup>3</sup> of acetonitrile. 40 cm<sup>3</sup> of ether is added, the precipitate is filtered off, rinsed with ether and dried for 16 hours under reduced pressure. After chromatography on silica (eluant: methylene chloride - methanol 94-6), 306 mg of expected product is obtained.

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-1,2-dimethylimidazo-[4,5-c]-pyridinium trifluoroacetate hydroiodide.

The operation is carried out as in Example 14 Stage B starting with 297 mg of product obtained in Stage A. 155 mg of expected product is obtained.

NMR (DMSO 400 MHz)

20	=N-O-CH-CO <sub>2</sub> H	: 5.40 (s1)
	and CH=CH-CH <sub>2</sub>	: 5.30 (s) 3H
	H <sub>6</sub>	: 5.13 (d)
	H <sub>7</sub>	: 5.75 (m)
25	C-NH-CH	: 9.63 (d), 9.65 (d)
	-CH-CH-CH <sub>2</sub>	: 6.98 (d, J=15.5) delta E
	-CH=CH-CH <sub>2</sub>	: 6.30 (d,t)
	the CH <sub>3</sub> 's	: 2.71 (s), 3.92 (s)
	imidazopyridine	: 8.28 to 9.48
30	aromatics and H <sub>5</sub> thiazole	: 6.66 to 6.85
	mobile H's	: 9.00, 9.08

EXAMPLE 21: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-2,3-dimethylimidazo-[4,5-c]-pyridinium trifluoroacetate hydroiodide.

STAGE A: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[[1-[3,4-bis-

[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenyl-methoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(paramethoxybenzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-2,3-dimethylimidazo-[4,5-c] pyridinium iodide.

The operation is carried out as indicated in Stage A of Example 20 using 1.92 g of product obtained as in Stage B of Example 11 and 303 mg of 2,3-dimethyl-4-aza benzimidazole. 877 mg of expected product is obtained.

10 STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[(2-amino-4-thiazolyl)-[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-2,3-dimethylimidazo-[4,5-c]-pyridinium trifluoroacetate hydroiodide.

15 The operation is carried out as in Stage B of Example 14 starting with 865 mg of product obtained in Stage A. 488 mg of expected product is obtained.

NMR (DMSO 400 MHz)

20 =N-O- $\overset{\gamma}{\text{CH}}$ -CO<sub>2</sub>H : 5.31 (s) 3H  
and CH=CH- $\text{CH}_2$  : 5.41 (l)

H<sub>6</sub> : 5.15 (d, resolved)

H<sub>7</sub> : 5.76

25 C-NH-CH : 9.53 (d), 9.60 (d)  
- $\text{CH}$ -CH-CH<sub>2</sub> : (d, J=15.5) delta E  
-CH= $\text{CH}$ -CH<sub>2</sub> : 6.34 (d,t)

the CH<sub>3</sub>'s : 2.75 (s), 3.94 (s)

imidazopyridine : 8.18 to 9.58

30 aromatics and H<sub>5</sub> thiazole : 6.65 to 6.86

mobile H's : 7.31 to 9.60

EXAMPLE 22: [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[(2-amino-4-thiazolyl)-[1-(3,4-dihydroxy phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-quinolinium trifluoroacetate hydroiodide.

STAGE A: [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[1-[3,4-bis-[(2-methoxy ethoxy)-methoxy]-phenyl]-2-[(diphenyl-methoxy)-2-

oxoethoxy]-imino] [2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(paramethoxybenzyloxy)-carbonyl]-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-quinolinium iodide.

- 5 The operation is carried out as in Stage B of Example 6 starting with 2.50 g of iodinated derivative prepared as in Stage B of Example 11 and 0.63 g of quinoline. 2.40 g of expected product is obtained which is purified by chromatography on silica (eluant: methylene chloride - 10 methanol 95-5).

STAGE B: [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7- [[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy phenyl)-2- hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-quinolinium

- 15 trifluoroacetate hydroiodide.

The operation is carried out as in Stage B of Example 14 using 1.65 g of the product obtained in Stage A and 0.94 g of expected product is obtained.

NMR (DMSO 400 MHz)

20



: 5.31 (s)

H<sub>6</sub>

: 5.14 (d)

H<sub>7</sub>

: 5.75 (m)

C-NH-CH

: 9.48 (d), 9.52 (d)

- 25 -CH-CH-CH<sub>2</sub>

: 6.97 (d, J=15) delta E

-CH=CH-CH<sub>2</sub>

: 5.89 (m)

H of the quinoline

: 8.07 to 9.59

aromatics and H<sub>5</sub> thiazole

: 6.64 to 6.77; 6.85 (s)

mobile H's

: 9.03 to 9.52

- 30 EXAMPLE 23: [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[2-amino-4-thiazolyl)-[[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-4-ethylthio pyridinium trifluoroacetate hydroiodide.

- 35 STAGE A: [6R-[3(E), 6alpha, 7beta (Z)]]-1-[3-[7-[[[1-[3,4-bis-[(2-methoxy-ethoxy)-methoxy]-phenyl]-2-[(diphenyl-methoxy)-2-oxoethoxy]-imino]-[2-[(triphenylmethyl)-amino]-4-thiazolyl]-acetyl]-amino]-2-[(paramethoxybenzyloxy)-carbonyl]-8-oxo-5-

thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-4-ethylthio pyridinium iodide.

The operation is carried out as in Stage B of Example 6 starting with 2.50 g of iodinated derivative prepared as in Stage B of Example 11 and 1 cm<sup>3</sup> of 4-ethylthio pyridine. 2.45 g of expected product is obtained which is purified by chromatography on silica (eluant: methylene chloride - methanol 95-5).

**STAGE B:** [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[2-amino-4-thiazolyl)-[1-(3,4-dihydroxy-phenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-4-ethylthio pyridinium trifluoroacetate hydroiodide.

The operation is carried out as in Stage B of Example 14 using 1.54 g of the product obtained in Stage A and 0.807 g of expected product is obtained.

NMR (DMSO 400 MHz)

$\text{=N-O-CH-CO}_2\text{H}$  : 5.32 (s)

20  $\text{H}_6$  : 5.16

$\text{H}_7$  : 5.77 (m)

$\text{C-NH-CH}$  : 9.47 (d)

$\text{-CH-CH-CH}_2\text{-}$  6.98 (d, J=16) delta E

25  $\text{-CH=CH-CH}_2\text{-}$  6.26 (d,t)

H of the pyridine : 7.97 to 8.69

aromatics and  $\text{H}_5$  thiazole : 6.67 to 6.78; 6.87 (s)

mobile H's : 9.04 to 13.80

**EXAMPLE 24:** Preparations for injection were made of formula:

30 - Product of Example 2 ..... 500 mg

- sterile aqueous excipient sufficient

quantity for ..... 5 cm<sup>3</sup>

#### ~~PHARMACOLOGICAL STUDY OF THE PRODUCTS OF THE INVENTION~~

In vitro activity, method of dilutions in solid medium.

35 A series of dishes is prepared into which an equal quantity of sterile nutritive medium is divided, containing increasing quantities of the product to be studied, then each dish is seeded with several bacterial strains.



**EXAMPLE 25:** the internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 7-[3-[7-[[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl]

5 furo[2,3-b]pyridinium (R) or (S) or an (R+S) mixture,

Stage A: p-methoxy benzyl [6R-[3(E), 6alpha, 7beta(Z)]]

7-[[[(diphenylmethoxy carbonyl) [3,4-bis[(2-methoxy ethoxy) methoxy] phenyl] methoxy] imino] [2-[(triphenylmethyl) amino] 4-thiazolyl] acetyl] amino] 3-(3-chloro 1-propenyl) 8-oxo

10 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl-2-carboxylate.

A suspension containing 3.75 g of

[[[(diphenylmethoxy-carbonyl) [3,4-bis[(2-methoxy ethoxy) methoxy] phenyl] methoxy] imino] [2-[(triphenylmethyl) amino] 4-thiazolyl] acetic acid syn isomer (described in the European

15 Patent EP 238061) and 1.81 g of p-methoxy benzyl 7-amino

3-(3-chloropropenyl) 8-oxo 5-thia 1-azabicyclo [4,2,0] oct-2-en-2-carboxylate (prepared as indicated in the European Patent EP 0 333 154) in dichloromethane is cooled down to 0°C,

and 0.920 g of N-(dimethylaminopropyl) N'-ethyl carbodiimide

20 hydrochloride is added. The solution obtained is kept at 0°C

under agitation for 30 minutes. The organic phase is washed with an aqueous solution of sodium chloride, dried and the solvents are eliminated. After chromatographing the residue on silica (eluant: methylene chloride - ether 85-15) and

25 concretion in isopropyl ether, 4.5-6 g of expected product is obtained.

NMR (CDCl<sub>3</sub> 400 MHz in ppm)

5.10 to 5.32: CO<sub>2</sub>-CH<sub>2</sub>-Ar (Ar: aromatic ring)

3.80: Ar-O-CH<sub>3</sub>

30 Stage B: p-methoxy benzyl [6R-[3(E), 6alpha, 7beta(Z)]]

7-[[[(diphenylmethoxy carbonyl) [3,4-bis[(2-methoxy ethoxy) methoxy] phenyl] methoxy] imino] [2-[(triphenylmethyl) amino] 4-thiazolyl] acetyl] amino] 3-(3-iodo 1-propenyl) 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl-2-carboxylate.

35 A mixture of the product obtained in Stage A, 10 cm<sup>3</sup> of acetone and 341 mg of sodium iodide and approximately 10 mg of iodine is agitated for one hour at ambient temperature, the solvent is evaporated off then the residue is taken up in 80



cm<sup>3</sup> of dichloromethane. The organic phase is washed with an aqueous solution of sodium thiosulphate then with water. After drying, the solvents are eliminated, the residue is chromatographed on silica [eluant: dichloromethane - ethyl acetate (8-2)] and 853 mg of expected product is obtained.

NMR of the proton, (CDCl<sub>3</sub> 300MHz)

6.9 to 7.35: -CH=CH-CH<sub>2</sub>-I, Ar-H

6.13 (d,t J=15 and 8): -CH=CH-CH<sub>2</sub>-I, E isomerism

4.0 (d): -CH=CH-CH<sub>2</sub>-I

- 10 **Stage C:** (±)(cis)(Z) 7-[3-[7-[[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2(E)-propenyl] furo[2,3-b]pyridinium iodide.

1.928 g of the product prepared in Stage B, 0.365 g of furo[2,3-b]pyridine and 2 cm<sup>3</sup> of dichloromethane are agitated for two hours and 30 minutes, 40 cm<sup>3</sup> of sulphuric ether is added, the precipitate is isolated, rinsed with ether, dried and chromatographed on silica eluting with a dichloromethane - methanol (92-8) mixture; 0.5106 g of the expected product is collected. Rf = 0.38

NMR of the proton (CDCl<sub>3</sub>, 400 MHz, in ppm)

3.22 (s), 3.29 (s) and 3.35 (s): -O-CH<sub>2</sub>-O-CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>3</sub>

3.79 (s): Ar-OCH<sub>3</sub>

3.10 to 3.9: -S-CH<sub>2</sub>-C(CH=CH-)=C- and -O-CH<sub>2</sub>-O-CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>3</sub>

- 25 5.00 (d) and 5.04 (d): -CO-NH-CH(C=O)-CH(N-)-S-

5.15 to 5.35: -O-CH<sub>2</sub>-O-CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>3</sub>

5.32 (s): -(C=O)-O-CH<sub>2</sub>-Ar

5.79 (dd) and 5.85 (dd): -CO-NH-CH(C=O)-CH(N-)-S-

5.99 (resolved): Ar-CH(C=O)-O-

- 30 6.34 (m): -CH=CH-CH<sub>2</sub>-N<sup>+</sup>

6.77 (resolved): -S-CH-C(C=N-)-N=

6.84 to 7.45: Ar-H, -CH=CH-CH<sub>2</sub>-N<sup>+</sup> and the H in position 3 of the furo[2,3-b]pyridinium

7.87 (m): H in position 5 of the furo[2,3-b]pyridinium 8.03

- 35 (m): H in position 2 of the furo[2,3-b]pyridinium 8.35 (d): the -NH-'s

8.66 (m): H in positions 4 and 6 of furo[2,3-b]pyridinium

**Stage D:** the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]



7-[3-[7-[[2-amino 4-thiazolyl] [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] furo[2,3-b]-pyridinium (R) or (S) or an (R+S) mixture,

5 0.516 g of the product prepared in the previous stage and 5.1 cm<sup>3</sup> of a solution of trifluoroacetic acid with 10% anisole are agitated for one hour and fifteen minutes; then 30 cm<sup>3</sup> of sulphuric ether is added, agitation takes place again for one hour and 30 minutes, followed by filtering, rinsing and  
10 drying.

0.261 g of the desired product is collected.

NMR of the proton (DMSO, 400 MHz, in ppm)

3.50 to 3.78 (m): -S-CH<sub>3</sub>-C(CH=CH-)=C-

5.16 (d resolved): -CO-NH-CH(C=O)-CH(N-)-S-

15 5.31 (s): Ar-CH(C=O)-O-

5.58 (m): -CH=CH-CH<sub>2</sub>-N<sup>+</sup>

5.77 (m): -CO-NH-CH(C=O)-CH(N-)-S-

6.32 (m): -CH=CH-CH<sub>2</sub>-N<sup>+</sup>

6.65 to 6.80 (m): aromatic H's of the (3,4-dihydroxy phenyl)

20 (Ar-H)

6.85 (s): -S-CH-C(C=N-)-N=

7.07 (d resolved): -CH=CH-CH<sub>2</sub>-N<sup>+</sup>

7.52 (d): H in position 3 of the furo[2,3-b]pyridinium 7.98

(dd): H in position 5 of the furo[2,3-b]pyridinium 8.61 (d): H  
25 in position 2 of the furo[2,3-b]pyridinium 8.89 (dl) and 8.93  
(d): H in positions 4 and 6 of the  
furo[2,3-b]pyridinium

7.31 (sl) (2 H) and 9.04 (m) (2 H): mobile H's

9.53 (d) and 9.61 (d): -CO-NH-CH(C=O)-CH(N-)-S-

30 **EXAMPLE 26:** The internal salt of [6R-[3(E), 6alpha, 7beta (Z)]]  
4-[3-[7-[[2-amino 4-thiazolyl] [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] furo[3,2-b]-pyridinium (R) or (S) or an (R+S) mixture

35 By operating in a similar manner to that of Example 25, using furo[3,2-b]pyridine as quaternization agent, the desired product is obtained.

NMR of the proton (DMSO, 400 MHz, in ppm)





- S-CH<sub>2</sub>-C(CH=CH-)=C- masked
- 5.14 (d resolved): -CO-NH-CH(C=O)-CH(N-)-S-
- 5.32 (s): Ar-CH(C=O)-O-
- 5.61 (m): -CH=CH-CH<sub>2</sub>-N<sup>+</sup>
- 5 5.76 (m): -CO-NH-CH(C=O)-CH(N-)-S-
- 6.30 (m): -CH=CH-CH<sub>2</sub>-N<sup>+</sup> E isomer
- 6.6 to 6.78 (m): Ar-H
- 6.86 (s): -S-CH-C(C=N-)-N=
- 7.02 (d resolved): -CH=CH-CH<sub>2</sub>-N<sup>+</sup>
- 10 7.78 (sl): H in position 3 of the furo[3,2-b]pyridinium 8.06  
(dd): H in position 6 of the furo[3,2-b]pyridinium 8.92 (d): H  
in position 2 of the furo[3,2-b]pyridinium 8.97 (d) to 9.04  
(m): H in positions 5 and 7 of the  
furo[3,2-b]pyridinium
- 15 9.0 (m): mobile H's
- 9.48 (d) and 9.56 (d): -CO-NH-CH(C=O)-CH(N-)-S-
- EXAMPLE 27:** the internal salt of (S)(cis)(Z) 7-[3-[7-[[2-amino  
4-thiazolyl] [[carboxy (3,4-dihydroxy phenyl) methoxy] imino]  
acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabi-cycle[4,2,0]  
20 oct-2-3-yl] 2(E)-propenyl] thieno[2,3-b] pyridinium
- By operating in a similar manner to that of Example 25,  
using as starting product [(S)-(diphenylmethoxycarbonyl)  
[3,4-bis[(2-methoxy ethoxy) methoxy] phenyl] methoxy] imino]  
[2-[(triphenylmethyl) amino] 4-thiazolyl] acetic acid syn  
25 isomer (described in European Patents EP 0266060 and 0280521)  
and thieno[2,3-b]pyridine as quaternization agent, the desired  
product is obtained.
- R<sub>f</sub> = 0.5 [thin layer chromatography (TLC); eluant: acetone -  
water (4-1)]
- 30 Alpha<sub>D</sub> = -11.5° [concentration (c) = 0.1 in DMSO],  
NMR of the proton (DMSO, 400 MHz, in ppm)
- 3.51 (m): -S-CH<sub>2</sub>-C(CH=CH-)=C-
- 5.15 (d J=5): -CO-NH-CH(C=O)-CH(N-)-S-
- 5.32 (s): Ar-CH(C=O)-O-
- 35 5.67 (d, J=6): -CH=CH-CH<sub>2</sub>-N<sup>+</sup>
- 5.8 (dd, sl after exchange): -CO-NH-CH(C=O)-CH(N-)-S-
- 6.27 (dt J=16 and 6): -CH=CH-CH<sub>2</sub>-N<sup>+</sup> E isomer
- 6.6 to 6.87 (m): Ar-H and -S-CH-C(C=N-)-N=

7.13 (d J=6):  $-\underline{\text{CH}}=\text{CH}-\text{CH}_2-\text{N}^+$

7.89 (d):  $\underline{\text{H}}$  in position 3 of the thieno[2,3-b]pyridinium 8.15

(dd):  $\underline{\text{H}}$  in position 5 of the thieno[2,3-b]pyridinium 8.28 (d):

$\underline{\text{H}}$  in position 2 of the thieno[2,3-b]pyridinium 9.08 (d):  $\underline{\text{H}}$  in

5 position 4 of the thieno[2,3-b]pyridinium 9.22 (d):  $\underline{\text{H}}$  in

position 6 of the thieno[2,3-b]pyridinium 9.55 (d):

$-\text{CO}-\underline{\text{NH}}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$

**EXAMPLE 28:** the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]

1-[3-[7-[[2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy

10 phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia

1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 4-methoxy

pyridinium (R) or (S) or an (R+S) mixture,

By operating in a similar manner to that of Example 25,  
using 4-methoxy pyridine as quaternization agent, the desired

15 product is obtained.

NMR of the proton (DMSO, 400 MHz, in ppm)

3.72 (AB):  $-\text{S}-\underline{\text{CH}}_2-\text{C}(\text{CH}=\text{CH}-)=\text{C}-$

4.10 (s):  $\text{Ar}-\text{O}-\underline{\text{CH}}_3$

5.15 (d):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\underline{\text{CH}}(\text{N}-)-\text{S}-$

20 5.22 (l):  $-\text{CH}=\text{CH}-\underline{\text{CH}}_2-\text{N}^+$

5.32 (s):  $\text{Ar}-\underline{\text{CH}}(\text{C}=\text{O})-\text{O}-$

5.77 (m):  $-\text{CO}-\text{NH}-\underline{\text{CH}}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$

6.25 (m):  $-\text{CH}=\underline{\text{CH}}-\text{CH}_2-\text{N}^+$  E isomer

6.68 (dd), 6.74 (m) (2H) and 6.86 (s) (1H)=:  $\text{Ar}-\underline{\text{H}}$  and

25  $-\text{S}-\underline{\text{CH}}-\text{C}(\text{C}=\text{N}-)-\text{N}=-$

6.95 (d J=15.5):  $-\underline{\text{CH}}=\text{CH}-\text{CH}_2-\text{N}^+$

7.33:  $\text{NH}_2$

7.66 (d) and 8.83 (m): aromatic  $\underline{\text{H}}$ 's of 4-MeO pyridinium

9.0 (l), 9.5 (d) and 9.62 (d): mobile  $\underline{\text{H}}$ 's

30 **EXAMPLE 29:** the internal salt of [6R-[3(E), 6alpha, 7beta (Z)]]

1-[3-[7-[[2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy

phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia

1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 4-(methylthio)

pyridinium (R+S),

35 By operating in a similar manner to that of Example 25,

using 4-(methylthio) pyridine as quaternization agent, the

desired product is obtained.

NMR of the proton (DMSO, 300 MHz, in ppm)



- 2.72 (s): Ar-S-CH<sub>3</sub>  
 5.15 (d) and 5.18 (d): -CO-NH-CH(C=O)-CH(N-)-S-  
 5.22 (dl): -CH=CH-CH<sub>2</sub>-N<sup>+</sup>  
 5.32 (s): Ar-CH(C=O)-O-  
 5 5.77 (m, d resolved after exchange): -CO-NH-CH(C=O)-CH(N-)-S-  
 6.26 (m): -CH=CH-CH<sub>2</sub>-N<sup>+</sup> E isomer  
 6.65 (dd) to 6.87 (m) (4 H)=: Ar-H and -S-CH-C(C=N-)-N=  
 6.99 (d J=15 Hz): -CH=CH-CH<sub>2</sub>-N<sup>+</sup>  
 7.96 (d) and 8.70 (d): aromatic H's of 4-Mes pyridinium  
 10 9.55 (d) and 9.62 (d): -CO-NH-CH(C=O)-CH(N-)-S-  
 7.32 (m) and 9.06 (m): mobile H's

EXAMPLE 30: the internal salt of [6R-[3(E), 6alpha, 7beta  
 [Z-(R\*)]]] 1-[3-[7-[[2-amino 4-thiazolyl) [[carboxy (3,4-  
 dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy  
 15 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl]  
 4-(methylthio) pyridinium,

The product obtained in Example 29 is purified by HPLC on  
 a Microbondapack C<sub>18</sub>-300 (registered trademark) column of 10  
 microns and 0.019 m in diameter eluting with acetonitrile with  
 20 0.025% trifluoroacetic acid and in this way leads to the (R)  
 and (S) isomers (See following example).

NMR of the proton (DMSO, 300 MHz, in ppm)

- 2.71 (s): Ar-S-CH<sub>3</sub>  
 3.54 (d) and 3.79 (d): -S-CH<sub>2</sub>-C(CH=CH-)=C-  
 25 5.17 (d): -CO-NH-CH(C=O)-CH(N-)-S-  
 5.22 (l): -CH=CH-CH<sub>2</sub>-N<sup>+</sup>  
 5.32 (s): Ar-CH(C=O)-O-  
 5.77 (d, d): -CO-NH-CH(C=O)-CH(N-)-S-  
 6.27 (m): -CH=CH-CH<sub>2</sub>-N<sup>+</sup> E isomer  
 30 6.72 (d): H in position 5 of the (3,4-dihydroxy phenyl)  
 6.74 (s): -S-CH-C(C=N-)-N=  
 6.73 (d): H in position 6 of the (3,4-dihydroxy phenyl)  
 6.86 (d): H in position 2 of the (3,4-dihydroxy phenyl)  
 6.98 (d J=15.5 Hz): -CH=CH-CH<sub>2</sub>-N<sup>+</sup>  
 35 7.30 (l): -NH<sub>2</sub>  
 7.96 (d) and 8.71 (d): aromatic H's of 4-MeS pyridinium  
 9.62 (d): -CO-NH-CH(C=O)-CH(N-)-S-  
 9.00 and 9.09: mobile H's

- EXAMPLE 31:** the internal salt of [6R-[3(E), 6alpha, 7beta [2-(S\*)]]] 1-[3-[7-[[2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 4-(methylthio) pyridinium,
- NMR of the proton (DMSO, 300 MHz, in ppm)
- 2.72 (s): Ar-S-CH<sub>3</sub>
- 3.54 [AB]: -S-CH<sub>2</sub>-C(CH=CH-)=C-
- 5.14 (d): -CO-NH-CH(C=O)-CH(N-)-S-
- 10 5.22 (dl): -CH=CH-CH<sub>2</sub>-N<sup>+</sup>
- 5.32 (s): Ar-CH(C=O)-O-
- 5.79 (dd): -CO-NH-CH(C=O)-CH(N-)-S-
- 6.24 (dt): -CH=CH-CH<sub>2</sub>-N<sup>+</sup> E isomer
- 6.65 to 6.78 (m) (3H) and 6.87 (1H): Ar-H and -S-CH(C=N-)-N=
- 15 6.97 (d): -CH=CH-CH<sub>2</sub>-N<sup>+</sup>
- 7.30 (l): -NH<sub>2</sub>
- 7.96 (d) and 8.70 (d): aromatic H's of 4-MeS pyridinium
- 9.55 (d): -CO-NH-CH(C=O)-CH(N-)-S-
- 9.04 and 9.08: mobile H's
- 20 **EXAMPLE 32:** The internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 1-[3-[7-[[2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 2-(methylthio) pyridinium (R) or (S) or an (R+S) mixture,
- 25 NMR of the proton (DMSO, 300 MHz, in ppm)
- 2.87 (s): Ar-S-CH<sub>3</sub>
- 5.16 (d, resolved): -CO-NH-CH(C=O)-CH(N-)-S-
- 5.78 (d, resolved after exchange): -CO-NH-CH(C=O)-CH(N-)-S-
- 6.13: -CH=CH-CH<sub>2</sub>-N<sup>+</sup> E isomer
- 30 6.65 to 6.80: Ar-H
- 6.85: -S-CH(C=N-)-N=
- 6.85 (d resolved): -CH=CH-CH<sub>2</sub>-N<sup>+</sup>
- 7.32 and 9.05: -OH
- 7.84 (t) and 8.44 (t): aromatic H's in position 3 and 4 of
- 35 the 2-MeS pyridinium
- 8.04 (d): aromatic H in position 5 of the 2-MeS pyridinium
- 8.97 (d): aromatic H in position 2 of the 2-MeS pyridinium
- 9.57 (d resolved): -CO-NH-CH(C=O)-CH(N-)-S-



- EXAMPLE 33:** the internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 1-[3-[7-[[2-amino 4-thiazolyl] [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 4-(amino-carbonyl) pyridinium (R) or (S) or an (R+S) mixture,
- NMR of the proton (DMSO, 300 MHz, in ppm)
- 3.50 to 3.75 (m):  $-S-\underline{CH}_2-C(CH=CH-)=C-$
- 5.17 (d resolved):  $-CO-NH-CH(C=O)-CH(N-)-S-$
- 5.32 (s):  $Ar-CH(C=O)-O-$
- 10 5.44 (m):  $-CH=CH-\underline{CH}_2-N^+$
- 5.77 (m):  $-CO-NH-CH(C=O)-CH(N-)-S-$
- 6.29 (m):  $-CH=CH-\underline{CH}_2-N^+$  E isomer
- 6.66 to 6.78 (m) (3 H):  $Ar-H$
- 6.86 (s):  $-S-CH(C=N-)-N=$
- 15 7.06 (d,  $J=15.5$ ):  $-CH=CH-\underline{CH}_2-N^+$
- 8.44 (d):  $H$  in positions 3 and 5 of the pyridinium ring
- 8.67 (s) and 8.25 (s):  $(C=O)-NH_2$  slightly mobile
- 9.20 (d):  $H$  in positions 2 and 6 of the pyridinium ring
- 9.47 (d) and 9.54 (d):  $-CO-NH-CH(C=O)-CH(N-)-S-$
- 20 8.94 (m) (2 H) 7.24 (m) (2 H) and 12.85 (shoulder): mobile  $H$ 's

- EXAMPLE 34:** the internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 1-[3-[7-[[2-amino 4-thiazolyl] [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 3-(amino-carbonyl) pyridinium (R) or (S) or an (R+S) mixture
- NMR of the proton (DMSO, 300 MHz, in ppm)
- 3.50 to 3.80 (m):  $-S-\underline{CH}_2(CH=CH-)=C-$  masked
- 5.17 (d resolved):  $-CO-NH-CH(C=O)-CH(N-)-S-$
- 5.32 (s):  $Ar-CH(C=O)-O-$
- 30 5.44 (m):  $-CH=CH-\underline{CH}_2-N^+$
- 5.77 (m):  $-CO-NH-CH(C=O)-CH(N-)-S-$
- 6.30 (m):  $-CH=CH-\underline{CH}_2-N^+$  E isomer
- 6.64 to 6.90 (m) (4 H):  $Ar-H$  and  $-S-CH(C=N-)-N=$
- 7.08 (d  $J=15$ ):  $-CH=CH-\underline{CH}_2-N^+$
- 35 7.29 (3 H):  $=C-NH_2$
- 8.29 (t):  $H$  in position 5 of the pyridinium ring
- 8.36 (d):  $H$  in position 4 of the pyridinium ring
- 9.17 (d):  $H$  in position 6 of the pyridinium ring



- 9.47 (d): H in position 2 of the pyridinium ring
- 9.54 (d) and 9.62:  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}^-)-\text{S}-$
- 8.20 (s) and 8.61 (s): slightly mobile H's 9.02: mobile H's
- EXAMPLE 35: The internal salt of [6R-[3(E), 6alpha, 7beta  
 5 (Z)]] 6-amino 1-[3-[7-[[2-amino 4-thiazolyl] [[carboxy  
 (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino]  
 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl]  
 2-propenyl] quinolinium (R) or (S) or an (R+S) mixture,  
 NMR of the proton (DMSO, 400 MHz, in ppm)
- 10 5.13:  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}^-)-\text{S}-$   
 5.31 (d resolved):  $\text{Ar}-\text{CH}(\text{C}=\text{O})-\text{O}-$   
 5.65 to 5.80:  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$  and  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}^-)-\text{S}-$   
 6.32 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$  E isomer  
 6.65 to 7.0 (m) (5 H):  $\text{Ar}-\text{H}$ ,  $-\text{S}-\text{CH}-\text{C}(\text{C}=\text{N}^-)-\text{N}=\text{}$  and  
 15  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$
- 7.56 (d resolved): H in position 7 of the quinolinium ring  
 7.88 (m): H in position 3 of the quinolinium ring  
 8.19 (m): H in position 8 of the quinolinium ring  
 8.80 (d): H in position 4 of the quinolinium ring
- 20 9.0 (s):  
 9.53 (d) and 9.61 (d):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}^-)-\text{S}-$
- EXAMPLE 36: the internal salt of [6R-[3(E), 6alpha, 7beta  
 (Z)]] 3-amino 1-[3-[7-[[2-amino 4-thiazolyl] [[carboxy  
 (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino]  
 25 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl]  
 2-propenyl] quinolinium (R) or (S) or an (R+S) mixture,  
 NMR of the proton (DMSO, 300 MHz, in ppm)
- 5.14:  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}^-)-\text{S}-$   
 5.31 (s) and 5.32 (s):  $\text{Ar}-\text{CH}(\text{C}=\text{O})-\text{O}-$
- 30 5.60 to 5.85 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$  and  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}^-)-\text{S}-$   
 6.33 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$  E isomer  
 6.6 to 6.8 (m):  $\text{Ar}-\text{H}$ ,  
 6.86 (s):  $-\text{S}-\text{CH}-\text{C}(\text{C}=\text{N}^-)-\text{N}=\text{}$   
 6.98 (d resolved):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$
- 35 7.76 (m) (2 H), 8.1 (m) (1 H) and 8.25 (m) (1 H): H in  
 positions 5, 6, 7 and 8 of the quinolinium ring  
 8.03 (d): H in position 4 of the quinolinium ring  
 8.87 (sl): H in position 2 of the quinolinium ring



- 9.09 (m): mobile H's  
 9.53 (d) and 9.61 (d):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$   
**EXAMPLE 37:** the internal salt of [6R-[3 (E), 6alpha, 7beta (Z)]] 1-[3-[7-[[2-amino 4-thiazolyl] [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 3-methyl quinolinium (R) or (S) or an (R+S) mixture,  
 NMR of the proton (DMSO, 300 MHz, in ppm)  
 2.66 (s):  $-\text{CH}_3$  in position 3 of the quinolinium ring  
 10 3.50 (masked) and 3.75 (d):  $-\text{S}-\text{CH}_2(\text{CH}=\text{CH}-)=\text{C}-$   
 5.13 resolved:  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$   
 5.31 (s):  $\text{Ar}-\text{CH}(\text{C}=\text{O})-\text{O}-$   
 5.78 (m):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$   
 5.85 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$   
 15 6.36 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$  E isomer  
 6.62 to 6.8 (m) (3 H):  $\text{Ar}-\text{H}$   
 6.85 (s):  $-\text{S}-\text{CH}-\text{C}(\text{C}=\text{N}-)-\text{N}=\text{C}-$   
 7.00 (d resolved):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$   
 8.01 (t) and 8.19 (t): H in position 6 and 7 of the quinolinium ring  
 20 8.38 (d) and 8.50 (d): H in position 5 and 8 of the quinolinium ring  
 9.14 (sl) and 9.54 (sl): H in position 2 and 4 of the quinolinium ring  
 25 9.04 (m): mobile H's  
 9.53 (d) and 9.59 (d):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$   
**EXAMPLE 38:** the internal salt of [6R-[3 (E), 6alpha, 7beta (Z)]] 1-[3-[7-[[2-amino 4-thiazolyl] [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 4-methyl quinolinium (R) or (S) or an (R+S) mixture,  
 NMR of the proton (DMSO, 300 MHz, in ppm)  
 3.02 (s):  $-\text{CH}_3$  in position 4 of the quinolinium ring  
 3.45 to 3.80 (m):  $-\text{S}-\text{CH}_2-\text{C}(\text{CH}=\text{CH}-)=\text{C}-$   
 35 5.13 (d resolved):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$   
 5.31 (s):  $\text{Ar}-\text{CH}(\text{C}=\text{O})-\text{O}-$   
 5.75 (d, resolved after exchange):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$   
 5.80 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$

- 6.37 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$  E isomer  
 approximately 6.70 (m) (3 H): Ar-H
- 6.85 (s):  $-\text{S}-\text{CH}-\text{C}(\text{C}=\text{N}-)-\text{N}=\text{}$
- 6.96 (d resolved  $j=16\text{Hz}$ ):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$
- 5 8.06 (t) and 8.25 (t): H in position 6 and 7 of the quinolinium ring
- 8.11 (d): H in position 3 of the quinolinium ring
- 8.50 (2d): H in position 5 and 8 of the quinolinium ring
- 9.43 (d): H in position 2 of the quinolinium ring
- 10 7.30 (sl and 9.03 (sl): mobile H's ( $-\text{NH}_2$  and  $-\text{OH}$ )
- 9.51 (d) and 9.59 (d):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$
- EXAMPLE 39: the internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 1-[3-[7-[[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia
- 15 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 6-methyl quinolinium (R) or (S) or an (R+S) mixture,  
 NMR of the proton (DMSO, 300 MHz, in ppm)
- 2.62 (s):  $-\text{CH}_3$  in position 4 of the quinoleinium ring
- 3.50 (masked) and 3.74 (d):  $-\text{S}-\text{CH}_2-\text{C}(\text{CH}=\text{CH}-)=\text{C}-$
- 20 5.13 (d resolved):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$
- 5.31 (s): Ar- $\text{CH}(\text{C}=\text{O})-\text{O}-$
- 5.76 (d, resolved after exchange):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$
- 5.86 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$
- 6.35 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$  E isomer
- 25 6.85 (s resolved):  $-\text{S}-\text{CH}-\text{C}(\text{C}=\text{N}-)-\text{N}=\text{}$
- 6.94 (d resolved  $j=16\text{Hz}$ ):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$
- 8.10 to 8.45 (m) (4 H): H in position 3, 5, 7 and 8 of the quinolinium ring
- 9.21 (d) (1 H): H in position 4 of the quinolinium ring
- 30 9.50 (d): H in position 2 of the quinolinium ring
- 9.03 (m): mobile H's
- 9.50 (d) and 9.60 (d):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$
- EXAMPLE 40: the internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 1-[3-[7-[[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia
- 35 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 6-chloro quinolinium (R) or (S) or an (R+S) mixture,  
 NMR of the proton (DMSO, 300 MHz, in ppm)





- 3.60 (masked) and 3.75 (d):  $-S-CH_2(CH=CH-)=C-$   
 5.14:  $-CO-NH-CH(C=O)-CH(N-)-S-$   
 5.31 (s):  $Ar-CH(C=O)-O-$   
 5.76 (m):  $-CO-NH-CH(C=O)-CH(N-)-S-$   
 5 5.88 (m):  $-CH=CH-CH_2-N^+$   
 6.34 (m):  $-CH=CH-CH_2-N^+$  E isomer  
 6.85 (s):  $-S-CH-C(C=N-)-N=$   
 6.96 (d resolved):  $-CH=CH-CH_2-N^+$   
 6.62 to 6.80 (m) (3 H):  $Ar-H$   
 10 8.29 (m) and 8.59 (dd):  $H$  in positions 3, 7 and 8 of the quinolinium ring  
 8.69 (d):  $H$  in position 5 of the quinolinium ring  
 9.25 (d):  $H$  in position 4 of the quinolinium ring  
 9.59 (d):  $H$  in position 2 of the quinoleinium ring  
 15 9.04 (m): mobile  $H$ 's  
 9.52 (d) and 9.60 (d):  $-CO-NH-CH(C=O)-CH(N-)-S-$   
EXAMPLE 41: the internal salt of [6R-[3(E), 6alpha, 7beta (Z)]] 1-[3-[7-[[2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia  
 20 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 6-methoxy quinolinium (R) or (S) or an (R+S) mixture,  
 NMR of the proton (DMSO, 400 MHz, in ppm)  
 3.45 to 3.75 (m):  $-S-CH_2-C(CH=CH-)=C-$   
 4.00 (s):  $-OCH_3$  in position 6 of the quinolinium ring  
 25 5.12 (d resolved):  $-CO-NH-CH(C=O)-CH(N-)-S-$   
 5.31 (s):  $Ar-CH(C=O)-O-$   
 5.74 (dd resolved):  $-CO-NH-CH(C=O)-CH(N-)-S-$   
 5.84 (m):  $-CH=CH-CH_2-N^+$   
 6.35 (m):  $-CH=CH-CH_2-N^+$  E isomer  
 30 6.65 to 6.80 (m):  $Ar-H$   
 6.85 (s):  $-S-CH-C(C=N-)-N=$   
 6.93 (d resolved  $J=16Hz$ ):  $-CH=CH-CH_2-N^+$   
 7.89 (dd):  $H$  in position 7 of the quinolinium ring  
 7.90 (sl):  $H$  in position 5 of the quinolinium ring  
 35 8.15 (dd):  $H$  in position 3 of the quinolinium ring  
 8.46 (dd):  $H$  in position 4 of the quinolinium ring  
 9.13 (d):  $H$  in position 8 of the quinolinium ring  
 9.37 (d):  $H$  in position 2 of the quinolinium ring



- 7.27 (m) (2 H) and 8.94 (m) (2 H): mobile H's  
 9.45 (d) and 9.52 (d):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$   
EXAMPLE 42: the internal salt of [6R-[3(E), 6alpha, 7beta  
 (Z)]] 3-[3-[7-[[2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy  
 5 phenyl) methoxy] imino] acetyl] amino] 2-carboxy 3-oxo 5-thia  
 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] thiazolium (R)  
 or (S) or an (R+S) mixture,  
 NMR of the proton (DMSO, 400 MHz, in ppm)  
 3.40 3.80 (m):  $-\text{S}-\text{CH}_2-\text{C}(\text{CH}=\text{CH}-)=\text{C}-$   
 10 5.16 (d resolved):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$   
 5.33 (m) (3 H):  $\text{Ar}-\text{CH}(\text{C}=\text{O})-\text{O}-$  and  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$   
 5.77 (m):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$   
 6.26 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$  E isomer  
 6.65 to 6.77 (m):  $\text{Ar}-\text{H}$   
 15 6.87 (s):  $-\text{S}-\text{CH}-\text{C}(\text{C}=\text{N}-)-\text{N}=\text{}$   
 6.97 (d resolved):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$   
 7.30 (s) (2 H): mobile H's  
 8.36 (s) and 8.52 (s): H in position 4 and 5 of the  
 thiazolium ring 9.00 (s), 9.08 (s), 9.09 (s) and  
 20 9.64 (s): mobile 2 H's  
 9.54 (d) and 9.62 (d):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$   
 10.21 (s): H in position 2 of the thiazolium ring  
EXAMPLE 43: the internal salt of [6R-[3(E), 6alpha, 7beta  
 (Z)]] 1-[3-[7-[[2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy  
 25 phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia  
 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 3-methyl  
 imidazolium (R) or (S) or an (R+S) mixture,  
 NMR of the proton (DMSO, 400 MHz, in ppm)  
 3.50 to 3.80:  $-\text{S}-\text{CH}_2-\text{C}(\text{CH}=\text{CH}-)=\text{C}-$   
 30 3.86 (s):  $-\text{CH}_3$  in position 3 of the imidazolium ring  
 4.97 (d):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$   
 5.16 (d resolved):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$   
 5.33 (s):  $\text{Ar}-\text{CH}(\text{C}=\text{O})-\text{O}-$   
 5.79 (m):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$   
 35 6.18 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$  E isomer  
 6.75 to 7.00 (m):  $\text{Ar}-\text{H}$ ,  $-\text{S}-\text{CH}-\text{C}(\text{C}=\text{N}-)-\text{N}=\text{}$  and  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$   
 7.28:  $\text{NH}_2$   
 7.71 (s) (2 H): H in position 2 and 3 of the imidazolium ring

8.96 (wide), 12.81 (wide) and 13.68 (wide): mobile 2 H's 9.12 (s): H in position 5 of the imidazolium ring

9.47 (d) and 9.54 (d):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$

EXAMPLE 44: the internal salt of ( $\pm$ )(cis)(Z) 1-[3-[7-

5 [[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2(E)-propenyl] imidazo [1,2-b] pyridazinium (R) or (S) or an (R+S) mixture, NMR of the proton (DMSO, 400 MHz, in ppm)

10 (1 H) masked and approximately 3.70 (d) (1 H):

$-\text{S}-\text{CH}_2-\text{C}(\text{CH}=\text{CH}-)=\text{C}-$

5.15 (d resolved):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$

5.25 to 5.45 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$  and  $\text{Ar}-\text{CH}(\text{C}=\text{O})-\text{O}-$

5.77 (m, d resolved after exchange):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$

15 6.25 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$  E isomer

6.65 to 6.86 (m):  $\text{Ar}-\text{H}$  and  $-\text{S}-\text{CH}-\text{C}(\text{C}=\text{N}-)-\text{N}=\text{N}-$

6.96 (dl  $J=16\text{Hz}$ ):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$

7.34 (m) and 9.05 (m): mobile H's

8.00 (dd): H in position 3 of the imidazo[1,2-b]pyridazinium ring

20 8.54 (sl) and 8.88 (sl): H in position 6 and 7 of the imidazo[1,2-b]pyridazinium ring

8.82 (d): H in position 4 of the imidazo[1,2-b]pyridazinium ring

25 9.12 (d): H in position 2 of the imidazo[1,2-b]pyridazinium ring

9.55 (d) and 9.60 (d):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$

EXAMPLE 45: the internal salt of ( $\pm$ )(cis)(Z) 1-[3-[7-

-[[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl)

30 methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2 (E)-propenyl] imidazo-[1,2-a]pyridinium (R) or (S) or an (R+S) mixture, NMR of the proton (DMSO, 300 MHz, in ppm)

3.55 (m) (masked):  $-\text{S}-\text{CH}_2-\text{C}(\text{CH}=\text{CH}-)=\text{C}-$

35 5.15 (m):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$

5.29 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$

5.32 (s):  $\text{Ar}-\text{CH}(\text{C}=\text{O})-\text{O}-$

5.74 (m):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$  cis isomerism



6.25 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$  E isomer  
 6.68 to 6.92: Ar-H,  $-\text{S}-\text{CH}-\text{C}(\text{C}=\text{N})-\text{N}=\text{}$  and  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$   
 7.33 (s), 9.03 (s), 9.56 (d resolved) and 12.80: mobile H's  
 7.57 (t) (1 H), 8.06 (t) (1 H), 8.20 (d) (1 H), 8.29 (s) (1  
 5 H), 8.45 (s) (1 H) and 8.97 (d) (1 H): H of the imidazo  
 [1,2-a]pyridinium ring

**EXAMPLE 46:** The internal salt of (+)(cis)(Z) 2-[3-[7--  
 [[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl)  
 methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia  
 10 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2(E)-propenyl] imidazo-  
 [1,5-a]pyridinium (R) or (S) or an (R+S) mixture,  
 NMR of the proton (DMSO, 300 MHz, in ppm)  
 3.40 to 3.80:  $-\text{S}-\text{CH}_2-\text{C}(\text{CH}=\text{CH}-)=\text{C}-$   
 5.17 (m):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$   
 15 5.18 to 5.32:  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$  and Ar-CH(C=O)-O-  
 5.76 (m):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$  cis isomerism  
 6.28 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$  E isomer  
 6.68 to 6.86: Ar-H and  $-\text{S}-\text{CH}-\text{C}(\text{C}=\text{N})-\text{N}=\text{}$   
 7.04 (d J=15.5):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$   
 20 7.29, 9.0 to 9.08, 9.54 and 12.56: mobile H's  
 7.19 (t) and 7.25 (t): H in position 6 and 7 of the imidazo  
 [1,5-a]pyridinium ring  
 7.86 (d): H in position 8 of the imidazo[1,5-a]pyridinium  
 ring 8.23 (d): H in position 1 of the imidazo[1,5-a]  
 25 pyridinium ring  
 9.02 (d): H in position 5 of the imidazo [1,5-a]pyridinium  
 ring  
 9.74 (s): H in position 3 of the imidazo [1,5-a]pyridinium  
 ring

30 **EXAMPLE 47:** The internal salt of [6R-[3(E), 6alpha, 7beta-  
 [Z(R\*)]]] 1-[3-[7-[[[(2-amino 4-thiazolyl) [[carboxy (3,4-  
 dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy  
 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2(E)-propenyl]  
 6,7-dihydro 5H-pyridinium,  
 35 **Stage A:** The internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]  
 1-[3-[7-[[[(diphenylmethoxycarbonyl) [3,4-bis[(2-methoxy  
 ethoxy) methoxy] phenyl] methoxy] imino] [2-[(tri-phenyl-  
 methyl) amino] 4-thiazolyl] acetyl] amino] 2-carboxy 8-oxo



5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2(E)-propenyl]  
6,7-dihydro 5H-pyrindinium, (R+S)

1.33 g of the iodine derivative prepared in Stage B of  
Example 25 and 0.585 cm<sup>3</sup> of cyclopentano[b]pyridine in a  
5 minimum quantity of dimethylsulphoxide (DMSO) are agitated for  
5 hours, the solvent is eliminated, the residue is washed and  
chromatographed eluting with a dichloromethane - methanol  
(9-1) mixture and in this way 1.07 g of the desired product is  
obtained.

10 **Stage B:** The internal salt of [6R-[3(E), 6alpha, 7beta(Z)]]  
1-[3-[7-[[2-amino 4-thiazolyl] [[carboxy (3,4-dihydroxy  
phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia  
1-azabicyclo[4,2,0]oct-2-en-3-yl] 2(E)-propenyl] 6,7-dihydro  
5H-pyrindinium,

15 By operating as in Stage D of Example 25, starting with  
1.053 g of the product prepared in the previous stage, 1.07 g  
of the expected product is obtained.

**Stage C:** The internal salt of [6R-[3(E), 6alpha, 7beta  
[Z(R\*)]]] 1-[3-[7-[[2-amino 4-thiazolyl] [[carboxy  
20 (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino]  
2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl]  
2(E)-propenyl] 6,7-dihydro 5H-pyrindinium,

The product obtained in Stage B is purified by HPLC on a  
Microbondapack C<sub>18</sub>-300 (registered trademark) column of 10  
25 microns and 0.0079 m in diameter eluting with acetonitrile  
with 0.025% of trifluoroacetic acid and in this way leads to  
the (R) and (S) isomers (See following example).

NMR of the proton (DMSO, 400 MHz, in ppm)

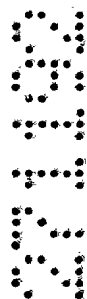
2.24 (m): the H's in position 6 of the 6,7-dihydro 5H-  
30 pyrindinium ring

3.15 (m) and 3.38 (masked): the H's in position 5 and 7 of  
the 6,7-dihydro 5H-pyrindinium  
ring

3.54 (d, J=17.5Hz) and 3.78 (d, J=17.5Hz): -S-CH<sub>2</sub>-C(CH=CH-)=C-  
35 5.17 (d, J=5): -CO-NH-CH(C=O)-CH(N-)-S-  
5.32 (m): -CH=CH-CH<sub>2</sub>-N<sup>+</sup> and Ar-CH(C=O)-O-  
5.75 (dd, J=5Hz and J=7.5Hz): -CO-NH-CH(C=O)-CH(N-)-S-  
6.24 (dt, J=16 and J=6.5 Hz): -CH=CH-CH<sub>2</sub>-N<sup>+</sup> E isomer



- 6.70 (d,  $J=8\text{Hz}$ ):  $\underline{\text{H}}$  in position 6 of the 3,4-dihydroxyphenyl radical
- 6.74 (s):  $-\text{S}-\underline{\text{CH}}-\text{C}(\text{C}=\text{N})-\text{N}=\text{}$
- 6.75 (dd,  $J=1.5$  and  $J=8\text{Hz}$ ):  $\underline{\text{H}}$  in position 5 of the 3,4-dihydroxyphenyl radical
- 5 6.86 (sl):  $\underline{\text{H}}$  in position 2 of the 3,4-dihydroxyphenyl radical
- 6.87 (d  $J=16$ ):  $-\underline{\text{CH}}=\text{CH}-\text{CH}_2-\text{N}^+$
- 7.25: Mobile  $\text{NH}_2$ 's
- 7.90 (dd,  $J=6$  and  $J=7.5$ ):  $\underline{\text{H}}$  in position 3 of the 6,7-dihydro 5H-pyrindinium ring
- 10 8.41 (d,  $J=7.5$ ):  $\underline{\text{H}}$  in position 4 of the 6,7-dihydro 5H-pyrindinium ring
- 8.75 (d,  $J=6$ ):  $\underline{\text{H}}$  in position 2 of the 6,7-dihydro 5H-pyrindinium ring
- 15 9.53 (d,  $J=7.5\text{Hz}$ ):  $-\text{CO}-\underline{\text{NH}}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N})-\text{S}-$
- 8.92, 9.00, 12.76 and 13.72: mobile  $\underline{\text{H}}$ 's
- EXAMPLE 48: The internal salt of [6R-[3(E), 6alpha, 7beta-[Z(S\*)]]] 1-[3-[7-[[2-amino 4-thiazolyl] [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy
- 20 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2(E)-propenyl] 6,7-dihydro 5H-pyrindinium,
- NMR of the proton (DMSO, 400 MHz, in ppm)
- 2.24 (m): the  $\underline{\text{H}}$ 's in position 6 of the 6,7-dihydro 5H-pyrindinium ring
- 25 3.15 (m) and 3.40: the  $\underline{\text{H}}$ 's in position 5 and 7 of the 6,7-dihydro 5H-pyrindinium ring
- 3.48 (d,  $J=17.5\text{Hz}$ ) and 3.63 (d,  $J=17.5\text{Hz}$ ):  $-\text{S}-\underline{\text{CH}}_2-\text{C}(\text{CH}=\text{CH})=\text{C}-$
- 5.14 (d,  $J=5$ ):  $-\text{CO}-\underline{\text{NH}}-\text{CH}(\text{C}=\text{O})-\underline{\text{CH}}(\text{N})-\text{S}-$
- 5.32 (m):  $-\text{CH}=\text{CH}-\underline{\text{CH}}_2-\text{N}^+$  and  $\text{Ar}-\underline{\text{CH}}(\text{C}=\text{O})-\text{O}-$
- 30 5.78 (dd,  $J=5\text{Hz}$  and  $J=7.5\text{Hz}$ ):  $-\text{CO}-\underline{\text{NH}}-\underline{\text{CH}}(\text{C}=\text{O})-\text{CH}(\text{N})-\text{S}-$
- 6.20 (dt,  $J=16$  and  $J=6\text{Hz}$ ):  $-\text{CH}=\underline{\text{CH}}-\text{CH}_2-\text{N}^+$  E isomer
- 6.68 (d,  $J=8\text{Hz}$ ):  $\underline{\text{H}}$  in position 6 of the 3,4-dihydroxyphenyl radical
- 6.75 (dd,  $J=2$  and  $J=8\text{Hz}$ ):  $\underline{\text{H}}$  in position 5 of the 3,4-dihydroxyphenyl radical
- 35 6.78 (s):  $-\text{S}-\underline{\text{CH}}-\text{C}(\text{C}=\text{N})-\text{N}=\text{}$
- 6.87 (d,  $J=2\text{Hz}$ ):  $\underline{\text{H}}$  in position 2 of the 3,4-dihydroxyphenyl radical
- 6.87 (d  $J=16$ ):  $-\underline{\text{CH}}=\text{CH}-\text{CH}_2-\text{N}^+$



- 7.25: mobile  $\text{NH}_2$ 's
- 7.90 (dd,  $J=6$  and  $J=7.5$ ):  $\text{H}$  in position 3 of the 6,7-dihydro 5H-pyrindinium ring
- 8.42 (d,  $J=7.5$ ):  $\text{H}$  in position 4 of the 6,7-dihydro 5H-pyrindinium ring
- 5 8.75 (d,  $J=6$ ):  $\text{H}$  in position 2 of the 6,7-dihydro 5H-pyrindinium ring
- 9.46 (d,  $J=7.5\text{Hz}$ ):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$
- 8.98 (2 H), 9.00, 12.97 (1 H) and 13.69 (1 H): mobile  $\text{H}$ 's
- 10 EXAMPLE 49: the internal salt of [6R-[3(E), 6alpha, 7beta(Z)]] 1-[3-[7-[[2-amino 4-thiazolyl] [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 4-[(methoxy-imino) methyl] quinoleinium (R) or (S) or an (R+S) mixture,
- 15 NMR of the proton (DMSO, 300 MHz, in ppm)
- 3.47 (m):  $-\text{S}-\text{CH}_2-\text{C}(\text{CH}=\text{CH}-)=\text{C}-$
- 4.19 (s):  $-\text{CH}=\text{N}-\text{OCH}_3$  in position 4 of the quinolinium ring
- 5.14 (m):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$
- 5.31 (s):  $\text{Ar}-\text{CH}(\text{C}=\text{O})-\text{O}-$
- 20 5.75 (m):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$
- 5.89 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$
- 6.36 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$  E isomer
- 6.64 to 6.77 (m):  $\text{Ar}-\text{H}$
- 6.85 (s,d):  $-\text{S}-\text{CH}-\text{C}(\text{C}=\text{N}-)-\text{N}=\text{N}-$
- 25 6.99 (d resolved  $j=16\text{Hz}$ ):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$
- 7.31 (l):  $-\text{NH}_2$
- 8.09 (l) and 8.30 (t):  $\text{H}$  in position 6 and 7 of the quinolinium ring
- 8.41 (d):  $\text{H}$  in position 3 of the quinolinium ring
- 30 8.58 (d) and 8.96 (d):  $\text{H}$  in position 5 and 8 of the quinolinium ring
- 9.33 (s):  $-\text{CH}=\text{N}-\text{OCH}_3$  in position 4 of the quinolinium ring (E isomer)
- 9.52 (d,d):  $\text{H}$  in position 2 of the quinolinium ring
- 35 9.03 (l) and 9.60 (d): mobile  $\text{H}$ 's
- EXAMPLE 50: the internal salt of (+)(cis)(Z) 1-[3-[7-[[2-amino 4-thiazolyl] [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicy-

clo[4,2,0]oct-2-en-3-yl] 2(E)-propenyl] 1-methyl pyrrolidinium  
(R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)

2.10 (sl) and 3.45 (sl): H of the pyrrolidinium ring

5 2.99 (s):  $N^+-CH_3$

3.9 (m):  $-S-CH_2-C(CH=CH-)=C-$

4.11:  $-CH=CH-CH_2-N^+$

5.18 (m):  $-CO-NH-CH(C=O)-CH(N-)-S-$

5.33 (s):  $Ar-CH(C=O)-O-$

10 5.79 (m):  $-CO-NH-CH(C=O)-CH(N-)-S-$

6.17 (dt):  $-CH=CH-CH_2-N^+$  E isomer

6.65 to 6.85:  $Ar-H$  and  $-S-CH-C(C=N-)-N=$

7.05 (d,  $J=15Hz$ ):  $-CH=CH-CH_2-N^+$

EXAMPLE 51: the internal salt of [6R-[3(E), 6alpha, 7beta

15 (Z)]] 1-[3 [7-[[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 4-aza 1-azonia-bicyclo[2,2,2]octane (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)

20 3.14 and 3.35: H of the 4-aza 1-azoniabicyclo[2,2,2]octane ring

3.5 to 3.95:  $-S-CH_2-C(CH=CH-)=C-$

4.06:  $-CH=CH-CH_2-N^+$

5.20 (d, resolved):  $-CO-NH-CH(C=O)-CH(N-)-S-$

25 5.34 (s):  $Ar-CH(C=O)-O-$

5.80 (d, resolved):  $-CO-NH-CH(C=O)-CH(N-)-S-$

6.11:  $-CH=CH-CH_2-N^+$  E isomer

6.7 to 6.90:  $Ar-H$  and  $-S-CH-C(C=N-)-N=$

7.02 (d, resolved):  $-CH=CH-CH_2-N^+$

30 9.10 (d resolved):  $-CO-NH-CH(C=O)-CH(N-)-S-$

EXAMPLE 52: The internal salt of [6R-[3(E), 6alpha, 7beta

(Z)]] 1-[3-[7-[[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2-propenyl] 3-hydroxy 4-aza

35 1-azoniabicyclo[2,2,2]octane (R) or (S) or an (R+S) mixture,

$R_f = 0.5$  (eluant: acetone - water (4-1))

EXAMPLE 53: The internal salt of (+)(cis)(Z) 3-[7-[[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino]





acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0] oct-2-3-yl] N,N,N-trimethyl 2(E)-propen-1-aminium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)

- 5 2.99 (s) and 3.03 (s):  $-N^+(CH_3)_3$   
 4.05:  $-CH=CH-CH_2-N^+$   
 5.16 (d):  $-CO-NH-CH(C=O)-CH(N-)-S-$   
 5.33 (s):  $Ar-CH(C=O)-O-$   
 5.76 (d):  $-CO-NH-CH(C=O)-CH(N-)-S-$   
 10 6.04 (m):  $-CH=CH-CH_2-N^+$  E isomer  
 6.7 to 6.90:  $Ar-H$  and  $-S-CH-C(C=N-)-N=$   
 7.04 (d, resolved):  $-CH=CH-CH_2-N^+$   
 9.08 (d resolved):  $-CO-NH-CH(C=O)-CH(N-)-S-$

EXAMPLE 54: The internal salt of [6R-[3(E), 6alpha, 7beta

- 15 (Z)]] 3-[7-[[2-amino 4-thiazolyl] [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] N,N-dimethyl N-(2-hydroxy ethyl) 2-propen-1-aminium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)

- 20 3.05 (s):  $-N^+(CH_3)_2-CH_2-CH_2-OH$   
 3.38 and 3.87:  $-N^+(CH_3)_2-CH_2-CH_2-OH$   
 4.14 (d):  $-CH=CH-CH_2-N^+$   
 5.19 (d, resolved):  $-CO-NH-CH(C=O)-CH(N-)-S-$   
 5.80 (d, resolved):  $-CO-NH-CH(C=O)-CH(N-)-S-$   
 25 6.14:  $-CH=CH-CH_2-N^+$  E isomer  
 6.87:  $-S-CH-C(C=N-)-N=$   
 6.65 to 6.80:  $Ar-H$   
 7.03 (d, resolved):  $-CH=CH-CH_2-N^+$   
 7.36 and 9.05:  $-OH$

- 30 9.59 (d resolved):  $-CO-NH-CH(C=O)-CH(N-)-S-$

EXAMPLE 55: The internal salt of (+)(cis)(Z) N-(2-amino 2-oxo ethyl) 3-[7-[[2-amino 4-thiazolyl] [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0]oct-2-en-3-yl] N,N-dimethyl 2(E)-propen-1-aminium (R) or (S) or an (R+S) mixture,

NMR of the proton (DMSO, 300 MHz, in ppm)

- 3.19 (s):  $-N^+(CH_3)_2-CH_2-CO-NH_2$   
 4.01 (s):  $-N^+(CH_3)_2-CH_2-CO-NH_2$

- 4.27 (d):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$   
 5.19 (d):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}^-)-\text{S}-$   
 5.34 (s):  $\text{Ar}-\text{CH}(\text{C}=\text{O})-\text{O}-$   
 5.85 (m):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}^-)-\text{S}-$   
 5 6.13:  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$  E isomer  
 6.72 to 6.80:  $\text{Ar}-\text{H}$  and  $-\text{S}-\text{CH}-\text{C}(\text{C}=\text{N}^-)-\text{N}=\text{}$   
 7.03:  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$   
 7.33, 7.70, 7.94 and 9.04: mobile  $\text{H}$ 's  
 9.55 (d) and 9.62 (d):  $-\text{NH}-$
- 10 **EXAMPLE 56:** the internal salt of (+)(cis)(Z) 3-[7-[[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0] oct-2-en-3-yl] N-(cyanomethyl) N,N-dimethyl 2(E)-propen-1-aminium (R) or (S) or an (R+S) mixture,
- 15 NMR of the proton (DMSO, 300 MHz, in ppm)  
 3.19 (s):  $-\text{N}^+(\text{CH}_3)_2-\text{CH}_2-\text{CN}$   
 4.24 (d):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$   
 4.8 (s):  $-\text{N}^+(\text{CH}_3)_2-\text{CH}_2-\text{CN}$   
 5.20 (d):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}^-)-\text{S}-$
- 20 5.33 (s):  $\text{Ar}-\text{CH}(\text{C}=\text{O})-\text{O}-$   
 5.82 (m):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}^-)-\text{S}-$   
 6.13 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$  E isomer  
 6.65 to 6.80:  $\text{Ar}-\text{H}$   
 6.87:  $-\text{S}-\text{CH}-\text{C}(\text{C}=\text{N}^-)-\text{N}=\text{}$
- 25 7.10:  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$   
 7.79 (2 H), 9.07 (2 H): mobile  $\text{H}$ 's  
 9.54 (d):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}^-)-\text{S}-$
- EXAMPLE 57:** The internal salt of (+)(cis)(Z) 3-[7-[[[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl) methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia 1-azabicyclo[4,2,0] oct-2-en-3-yl] N,N-dimethyl N-[(2-methoxyimino) ethyl] 2(E)-propen-1-aminium (R) or (S) or an (R+S) mixture,
- 30 NMR of the proton (DMSO, 300 MHz, in ppm)  
 3.19 (s):  $-\text{N}^+(\text{CH}_3)_2-\text{CH}_2-\text{CH}=\text{N}-\text{O}-\text{CH}_3$
- 35 3.89 (s):  $-\text{N}^+(\text{CH}_3)_2-\text{CH}_2-\text{CH}=\text{N}-\text{O}-\text{CH}_3$   
 4.10 to 4.30 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$  and  $-\text{N}^+(\text{CH}_3)_2-\text{CH}_2-\text{CH}=\text{N}-\text{O}-\text{CH}_3$   
 5.20 (d):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}^-)-\text{S}-$   
 5.35 (s):  $\text{Ar}-\text{CH}(\text{C}=\text{O})-\text{O}-$

- 5.81 (m,d resolved after exchange):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$   
 6.14 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$  E isomer  
 6.7 to 6.88:  $\text{Ar}-\text{H}$  and  $-\text{S}-\text{CH}-\text{C}(\text{C}=\text{N}-)-\text{N}=\text{$   
 7.04:  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$   
 5 7.77 (m):  $-\text{N}^+(\text{CH}_3)_2-\text{CH}_2-\text{CH}=\text{N}-\text{O}-\text{CH}_3$   
 9.57 and 9.65:  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$   
EXAMPLE 58: the internal salt of ( $\pm$ )(cis)(Z) 1-[3-[7--  
 [[(2-amino 4-thiazolyl) [[carboxy (3,4-dihydroxy phenyl)  
 methoxy] imino] acetyl] amino] 2-carboxy 8-oxo 5-thia  
 10 1-azabicyclo[4,2,0]oct-2-en-3-yl] 2(E)-propenyl] imidazo  
 [1,2-a] pyrimidin-4-ium (R) or (S) or an (R+S) mixture,  
 NMR of the proton (DMSO, 300 MHz, in ppm)  
 3.66 (m) (masked):  $-\text{S}-\text{CH}_2-\text{C}(\text{CH}=\text{CH}-)=\text{C}-$   
 5.14 (d, resolved):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$   
 15 5.24 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$   
 5.31 (s):  $\text{Ar}-\text{CH}(\text{C}=\text{O})-\text{O}-$   
 5.74 (m):  $-\text{CO}-\text{NH}-\text{CH}(\text{C}=\text{O})-\text{CH}(\text{N}-)-\text{S}-$  cis isomerism  
 6.23 (m):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$  E isomer  
 6.65 to 6.84 (4 H):  $\text{Ar}-\text{H}$ , and  $-\text{S}-\text{CH}-\text{C}(\text{C}=\text{N}-)-\text{N}=\text{$   
 20 6.94 (d, resolved J=16):  $-\text{CH}=\text{CH}-\text{CH}_2-\text{N}^+$   
 7.31 (sl):  $-\text{NH}_2$   
 9.03 (m): mobile H's  
 7.76 (dd) (1 H): H in position 6 of the imidazo[1,2-a]-  
 pyrimidin-4-ium ring  
 25 8.39 (s): H in position 2 and 3 of the imidazo[1,2-a]-  
 pyrimidin-4-ium ring  
 9.14 (d, resolved) (1 H): H in position 7 of the imidazo-  
 [1,2-a]pyrimidin-4-ium ring  
 9.39 (d, resolved) (1 H): H in position 5 of the imidazo-  
 30 [1,2-a]pyrimidin-4-ium ring  
 Unless otherwise indicated, the products of Examples 31 to  
 58 mentioned previously were prepared by the method described  
 in Example 25, using the corresponding nitrogenous base.  
EXAMPLE 59: Preparations for injections of the following  
 35 formula were prepared:  
 - Product of Example 31. .... 500 mg  
 - Sterile aqueous excipient sufficient  
 quantity for ..... 5 cm<sup>3</sup>



**PHARMACOLOGICAL STUDY OF THE PRODUCTS OF THE INVENTION****Activity in vitro, method of dilutions in solid medium.**

A series of dishes are prepared in which the same quantity of sterile nutrient medium is distributed, containing 5 increasing quantities of the product to be studied, then each dish is sown with several bacterial strains.

After incubation for 24 hours in an incubator at 37°C, the growth inhibition is evaluated by the absence of any bacterial development, which allows the minimum inhibiting 10 concentrations (MIC) expressed in micrograms/cm<sup>3</sup> to be determined.

The results are expressed in MIC<sub>90</sub> which is the minimum concentration of antibiotic causing growth inhibition in 90% of the strains studied.

15      The following results were obtained:

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Compound example	Number of strains	Enterobacteria		Staphylococcus aureus oxacilline S 20	Proteus SPP 9	Pseudomonas Aeruginosa 40
		Cefotax.S 27	Cefotax.R 40			
2		0,3	5	0,6	0,15	1,25
4		0,3	5	1,25	0,3	5
9		0,6	10	1,2	0,6	2,5
12		0,3	10	0,6	0,3	10
16		0,6	10	1,2	0,6	2,5
17		0,6	10	1,2	0,6	1,2
18		0,15	2,5	0,3	0,3	2,5

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Product of Enterobacteries				
Example	Cloacae 1321E	Staphylococcus aureus SG 5 11	Proteus A 235	Pseudomonas Aeruginosa 1771 m
29	0.08	0.15	0.04	0.3
31	0.04	0.15	0.02	0.6
25	0.15	0.15	0.02	0.15
45	0.15	0.15	0.04	0.6

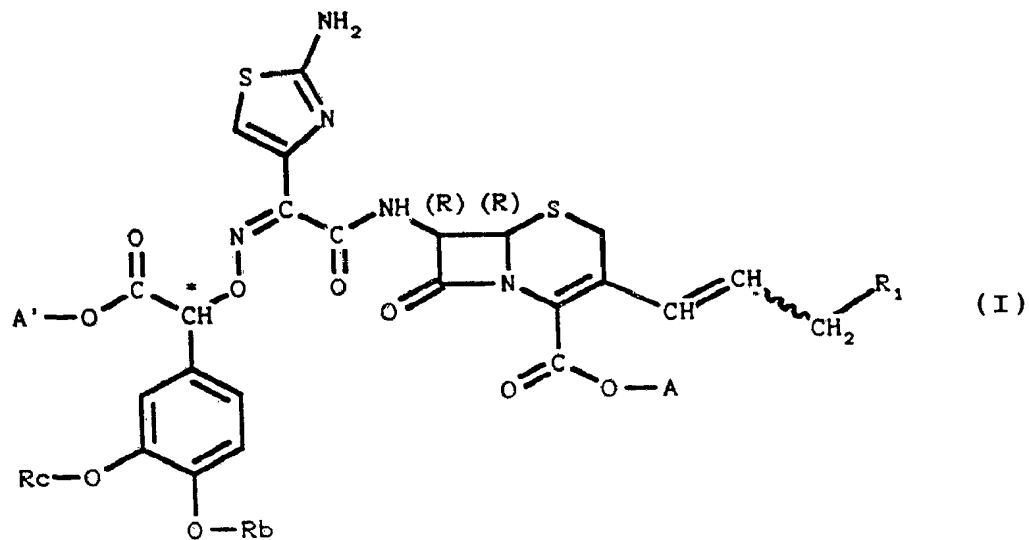
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The claims defining the invention are as follows:

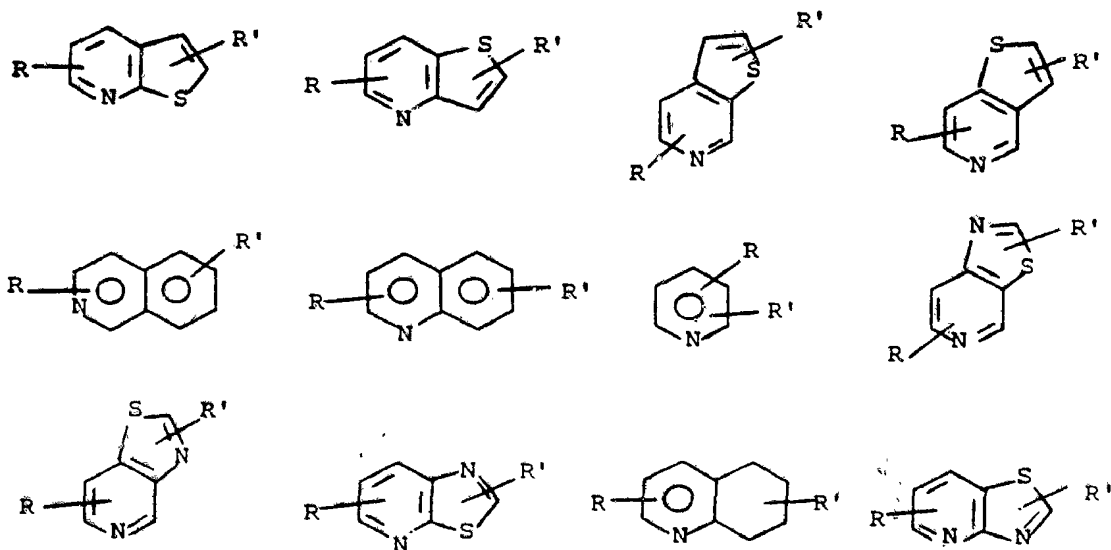
1.- The products of general formula (I):



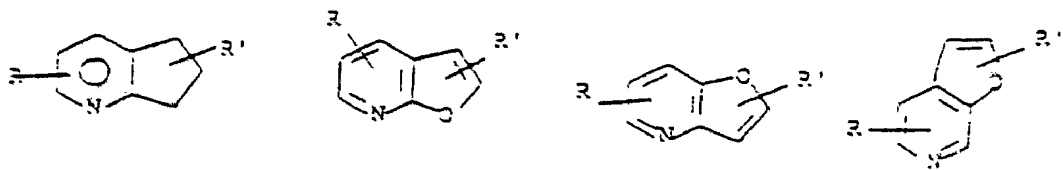
SYN isomer

syn isomer, in R or S form or in the form of an R, S, mixture, formula in which:

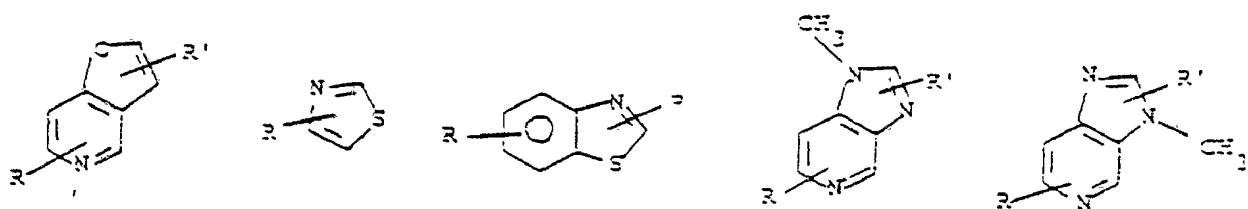
R<sub>1</sub> represents a radical chosen from the following radicals:



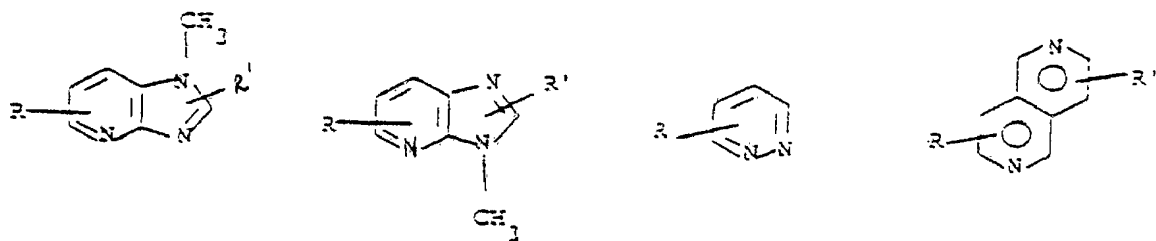
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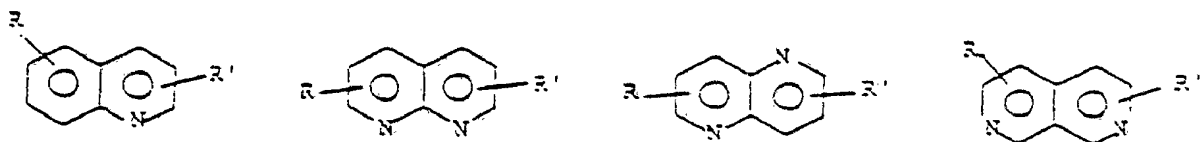
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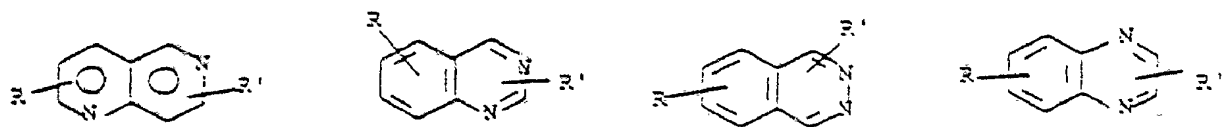
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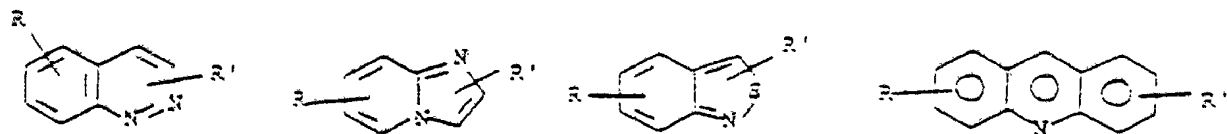
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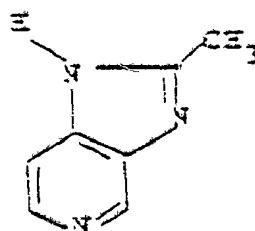
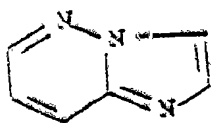
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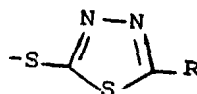
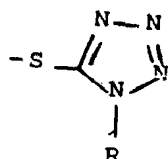
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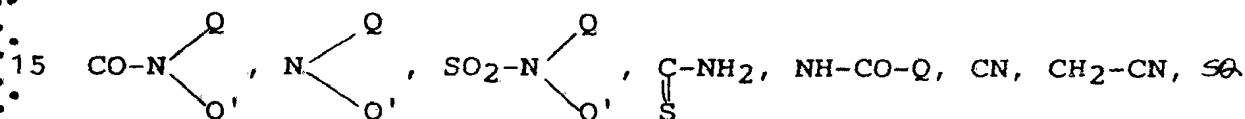



or  in the quaternary ammonium form or

5



10 in which R and R', identical or different, represent a hydrogen atom, an alkyl radical containing 1 to 4 carbon atoms, an alkoxy radical containing 1 to 4 carbon atoms, a halogen atom, one of the following radicals a CO<sub>2</sub>-Q,



CH<sub>2</sub>-SQ in which Q and Q', identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, P, P' and P'', identical or different, represent an alkyl radical containing at most 4 carbon atoms, optionally substituted by one of the substituents indicated above for R and R', the symbol  indicating that P and P' can optionally form, with the nitrogen atom to which they are linked, <sup>saturated</sup> a heterocycle with 5 or 6 links.

25 R<sub>B</sub> and R<sub>C</sub>, identical or different, represent a hydrogen atom or an acyl group,

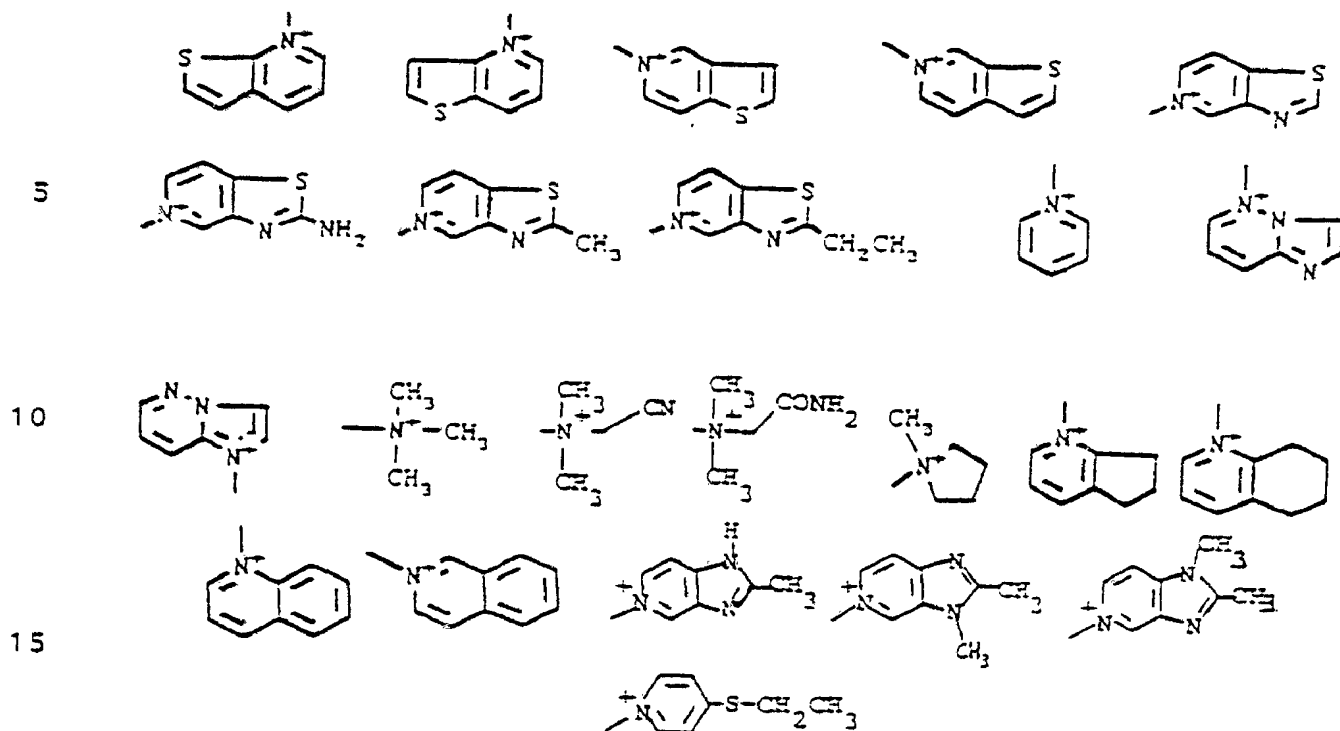
A and A', identical or different, represent a hydrogen atom, an equivalent of an alkali metal, an alkaline-earth metal, magnesium, ammonium or an amino organic base or A and A'

30 represent the remainder of an easily cleavable ester group or CO<sub>2</sub>A represents CO<sub>2</sub><sup>⊖</sup>; the wavy line means that the CH<sub>2</sub>R<sub>1</sub> group can be found in E or Z position as well as the salts of the products of formula (I) with the mineral or organic acids.

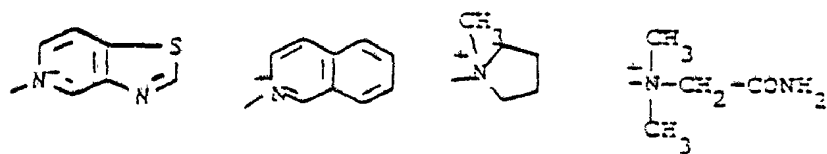
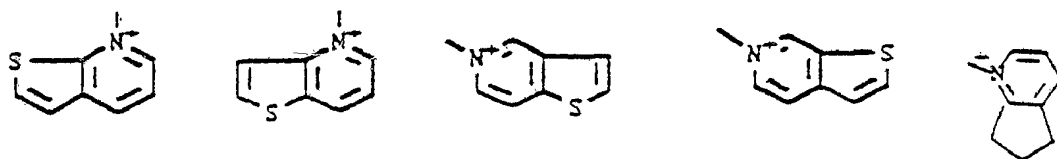
2.- The products of general formula (I) as defined in claim 1

35 in which R<sub>1</sub> is chosen from the following radicals:

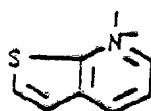




20 3.- The products of general formula (I) as defined in claim 1 or 2 in which R<sub>1</sub> is chosen from the following radicals:



35 preferably the radical:



4.- The product of general formula (I) according to claim 1 of which the name follows:

- [6R-[3(E), 6alpha, 7beta(Z)]]-5-[3-[7-[[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-

imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thiazolo-[4,5-c]-pyridinium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia,

amino organic bases, acids and its easily cleavable esters, - [6R-[3(E), 6alpha, 7beta(Z)]]-7-[3-[7-[[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-thieno-[2,3-b] pyridinium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters and particularly in the S form,

- [6R-[3(E), 6alpha, 7beta(Z)]]-2-[3-[7-[[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl] isoquinolinium in the R or S form or in the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic bases, acids and its easily cleavable esters,

- [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-[4,2,0]-oct-2-en-3-yl]-2-propenyl]-1-methyl pyrrolidinium in the R or S form or the form of an R, S mixture and in the form of an internal salt or a salt with alkali metals, alkaline-earth metals, magnesium, ammonia, amino organic

bases, acids and its easily cleavable esters,

- [6R-[3(E), 6alpha, 7beta(Z)]]-1-[3-[7-[[[(2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo-



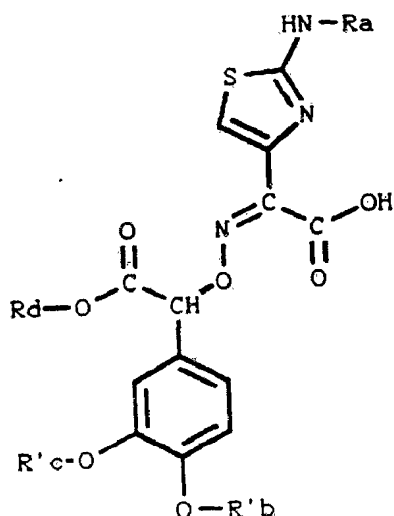
[4,2,0]-oct-2-en-3-yl]-2-propenyl]-6,7-dihydro-5H-pyridinium  
in the R or S form or in the form of an R, S mixture and in  
the form of an internal salt or a salt with alkali metals,  
alkaline-earth metals, magnesium, ammonia, amino organic

5 bases, acids and its easily cleavable esters,

- [6R-[3(E), 6alpha, 7beta(Z)]]-N-(2-amino-2-oxoethyl)-3-[7-  
[[2-amino-4-thiazolyl)-[[1-(3,4-dihydroxyphenyl)-2-hydroxy-  
2-oxoethoxy]-imino]-acetyl]-amino]-2-carboxy-8-oxo-5-thia-1-

10 aminium in the R or S form or in the form of an R, S mixture  
and in the form of an internal salt or a salt with alkali  
metals, alkaline-earth metals, magnesium, ammonia, amino  
organic bases, acids and its easily cleavable esters.

5.- Preparation process for the products of formula (I) as  
15 defined in claim 1, characterized in that a product of  
formula (II):



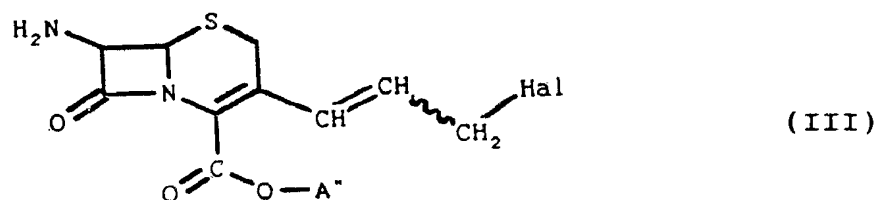
(II)

racemic or optically active syn isomer or a functional  
derivative of the product of formula (II), in which Ra

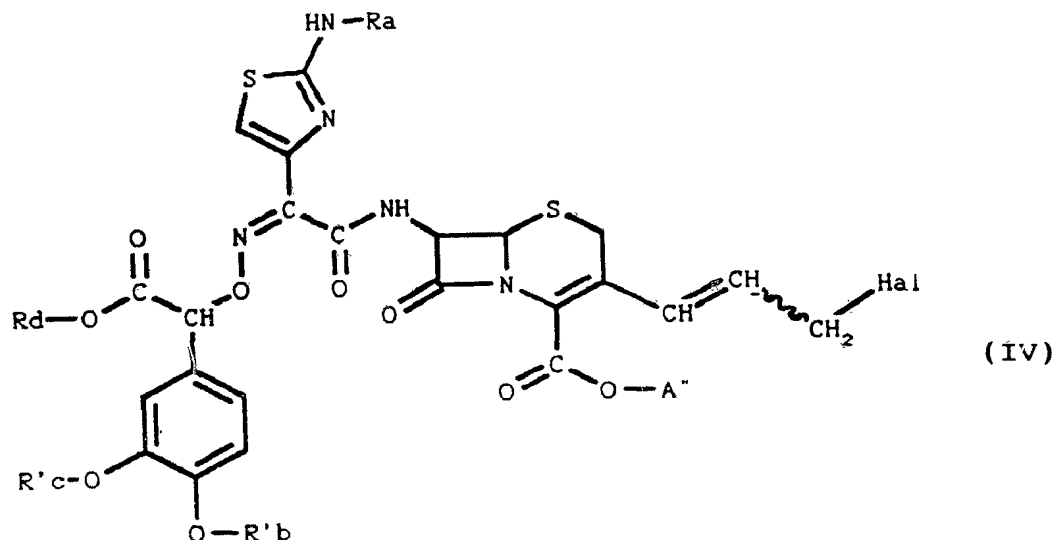
35 represents a hydrogen atom or a protective group of the amino  
radical, R'b and R'c, identical or different, represent a  
hydrogen atom or a protective group of the hydroxyl radical,  
Rd represents a hydrogen atom or the remainder of an easily



eliminable ester group, is reacted with a product of formula (III):

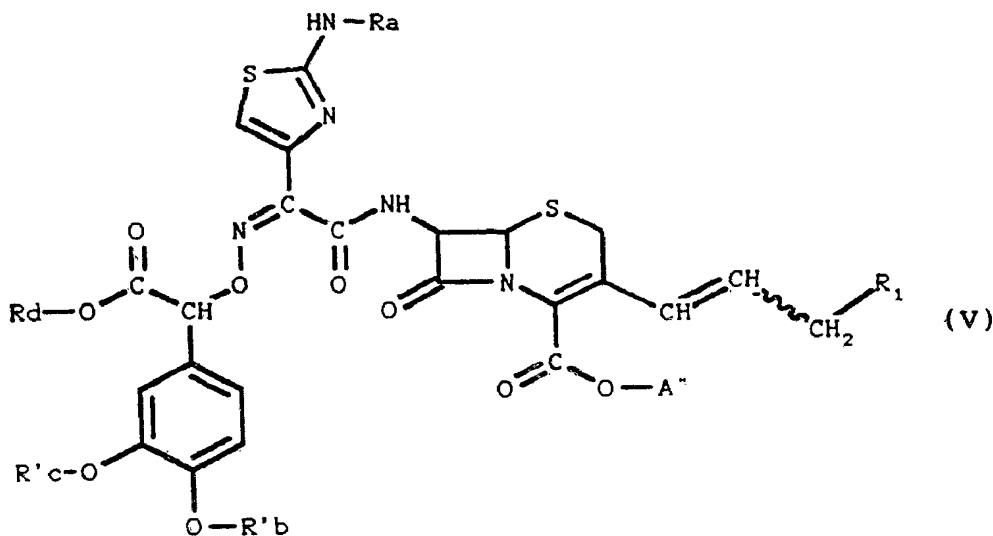


10 in which Hal represents a halogen atom, A'' represents a hydrogen atom or the remainder of an easily eliminable ester group and the wavy line indicates that the CH<sub>2</sub>Hal group can be found in E or Z position, in order to obtain a product of formula (IV):



20 which is reacted with a reagent capable of introducing the R<sub>1</sub> radical in order to obtain a product of formula (V):

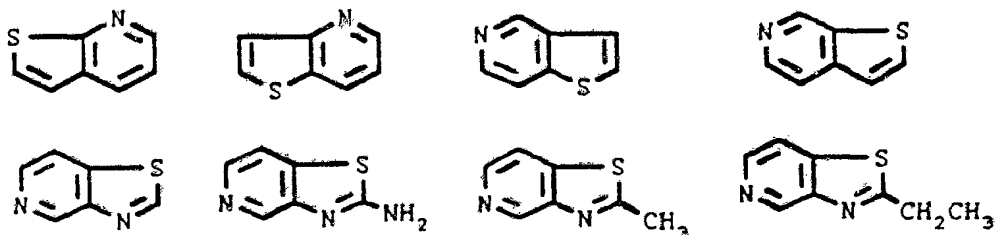


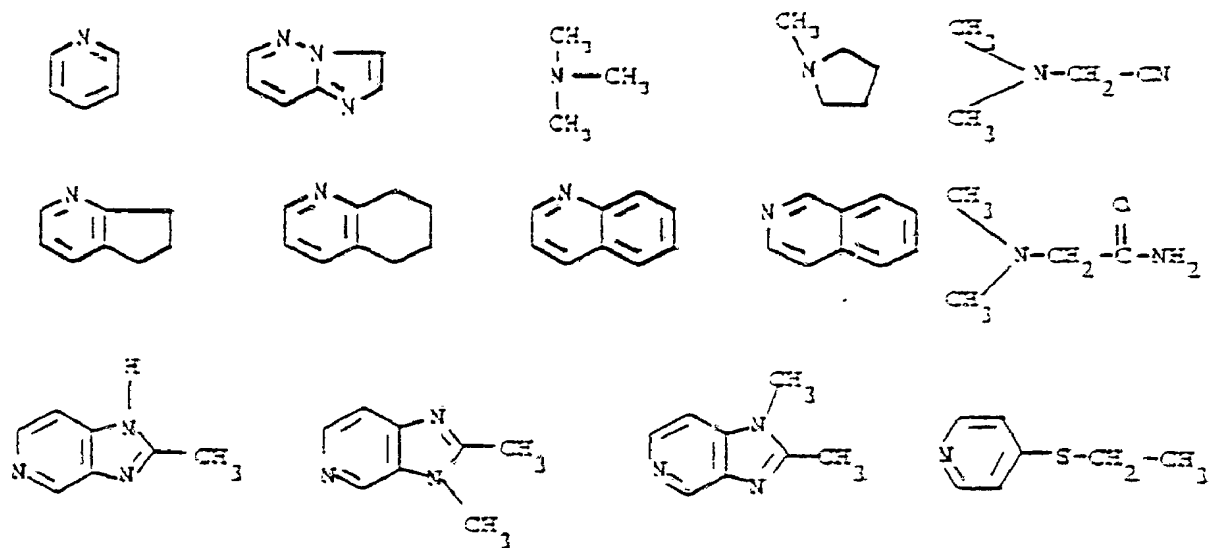


which, if desired, is separated into its E or Z isomers or the Z isomers are converted into E isomers and which products of formula (V), if necessary or if desired, are subjected to one or more of the following reactions, in any order:

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- 25
- 30
- cleaving, by hydrolysis or by the action of the thiourea, of all or part of the ester groups or protective groups of the amino radical or the hydroxyl radicals,
  - esterification or salification of the carboxylic radical or radicals by a base,
  - salification of the amino radical by an acid,
  - separation of products in the form of an R, S mixture into R or S.

6.- Preparation process according to claim 5 characterized in that the reagent capable of introducing the R<sub>1</sub> radical is chosen from the reagents of formulae:





7. Preparation process according to claim 5, wherein  $R_a$  represents a protective group of the amino radical in the products of formula (IV) and the products of formula (V).

8. Preparation process for the products of formula (I) as defined in claim 1 which process is substantially as herein described with reference to any one of the Examples.

9. Products of formula (I) whenever prepared by the process of any one of claims 5 to 8.

10. Products of general formula (I) as defined in claim 1, substantially as herein described with reference to any one of the Examples.

11. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 4 together with a pharmaceutically acceptable carrier, diluent, excipient and/or adjuvant.

12. A pharmaceutical composition as defined in claim 11, substantially as herein described with reference to Example 59.

~~13. A method of treating affections caused by sensitive germs notably staphylococcus in a patient/mammal requiring such treatment which method~~

13. The compound of formula (IV) and the compound of formula (V) as claimed in claim 5, in which  $R_a$  represents a protective group of the amino radical.

14. A method of treating affections caused by sensitive germs notably staphylococcus in a patient/mammal requiring such treatment which method  
5 comprises administering to said patient/mammal an effective amount of a compound of formula (I) as defined in any one of claims 1 to 4 or a composition as defined in claim 11 or claim 12.

15. The method according to claim 14, wherein said affections include staphylococcus septicemia, malignant staphylococcus of the face or skin, pyodermitis, septic or suppurating wounds, anthrax, phlegmons, erysipelas, acute  
10 primitive or post-influenza staphylococcus, bronchopneumonia, lung suppurations.

16. A method of treating affections caused by gram (-) bacteria in a patient/mammal requiring such treatment which method comprises administering to said patient/mammal an effective amount of a compound of formula (I) as  
15 defined in any one of claims 1 to 4 or a composition as defined in claim 11 or claim 12.

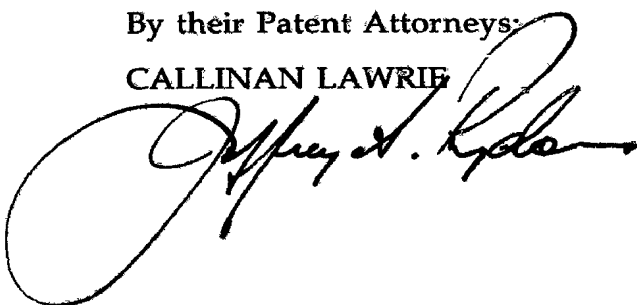
17. The method according to claim 16, wherein said affection includes colibacillosis.

DATED this 28th day of January 1994.

20 ROUSSEL-UCLAF

By their Patent Attorneys:

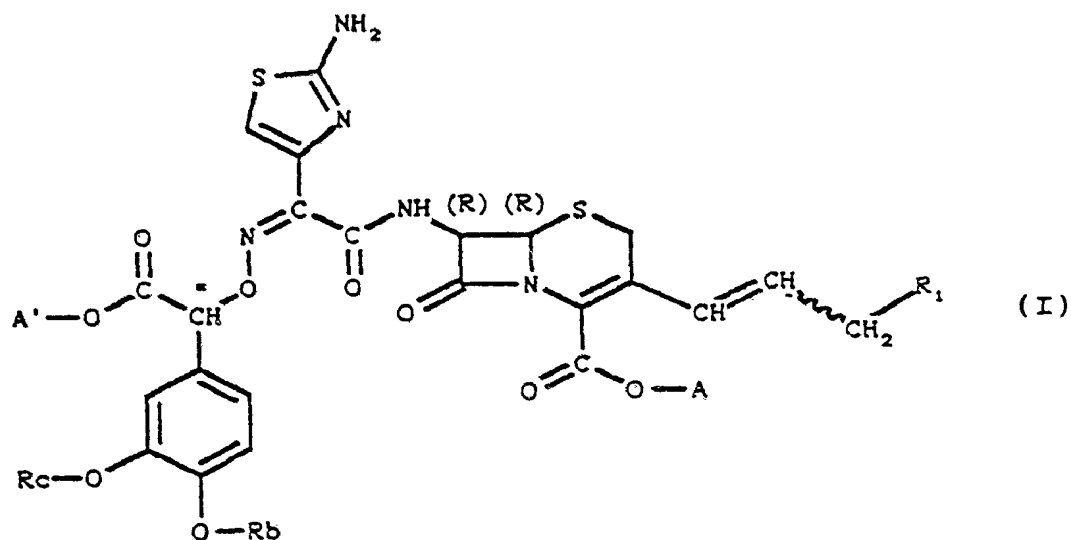
CALLINAN LAWRIE





# Abstract

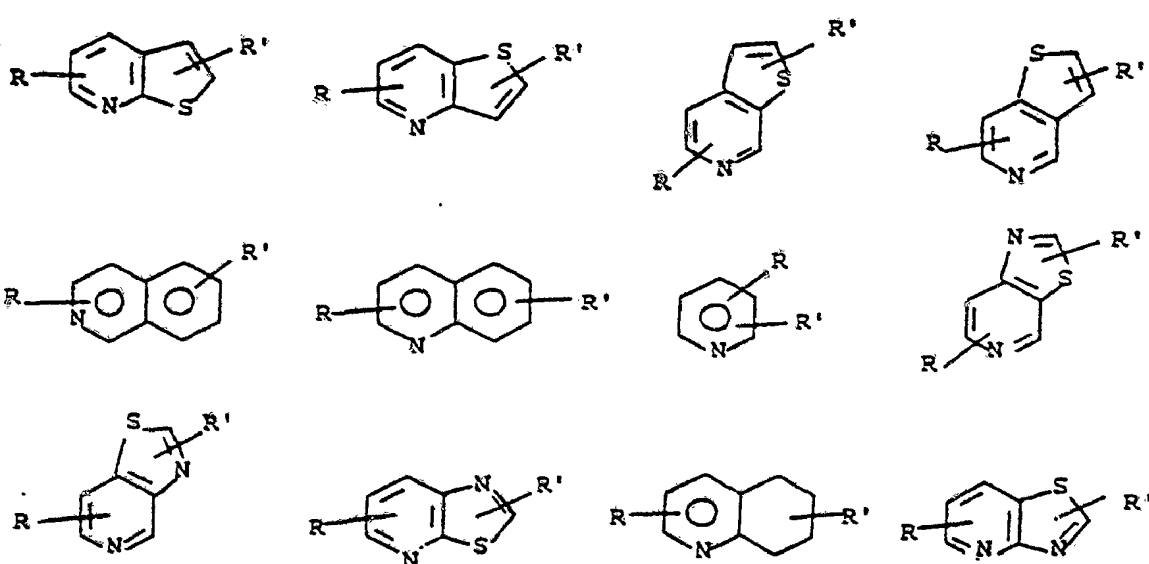
Cephalosporins of general formula (I):



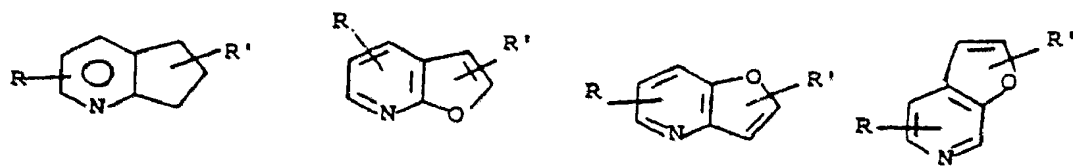
SYN isomer

syn isomer, in R or S form or in the form of an R, S, mixture, formula in which:

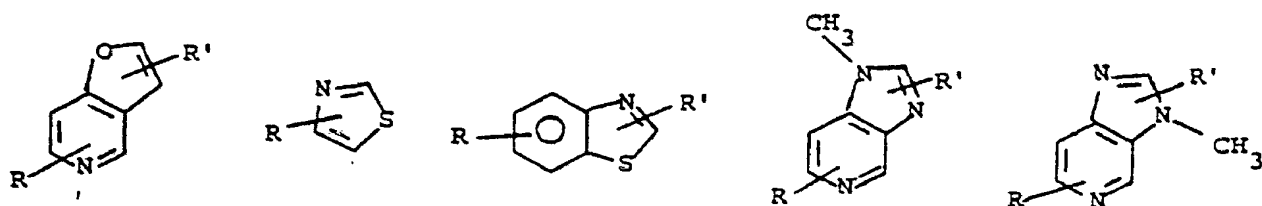
R<sub>1</sub> represents a radical chosen from the following radicals:



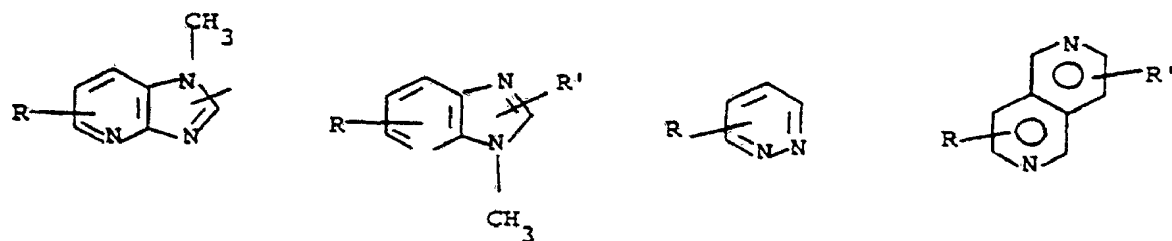
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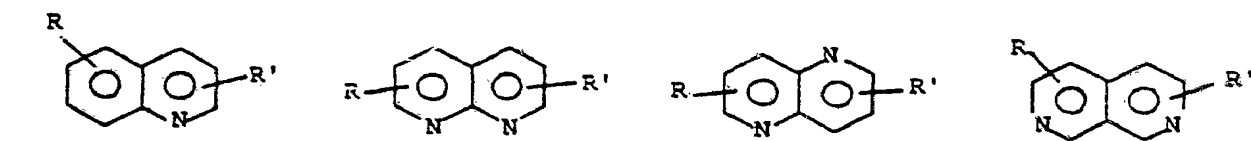


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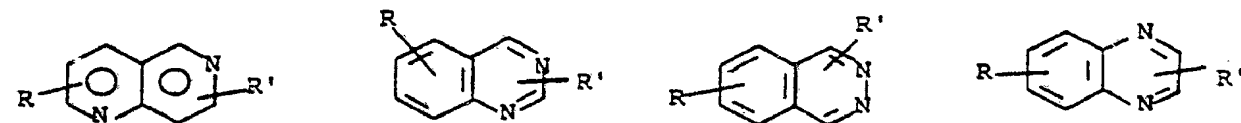


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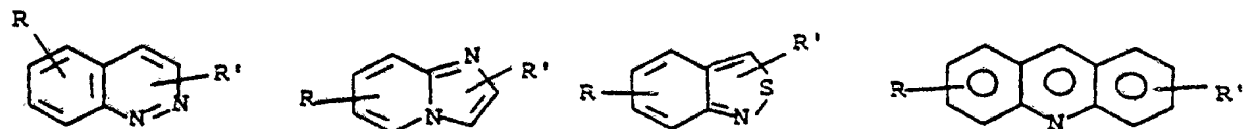
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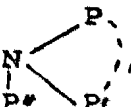


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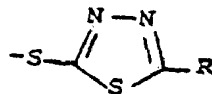
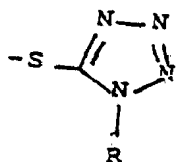


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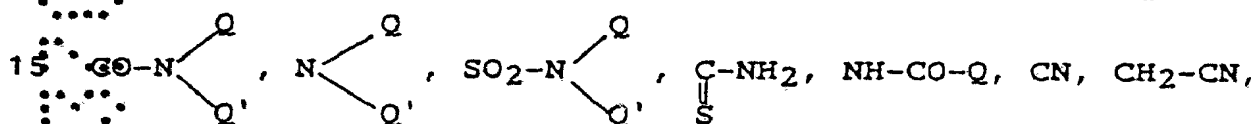


or  in the quaternary ammonium form or

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10 in which R and R', identical or different, represent a hydrogen atom, an alkyl radical containing 1 to 4 carbon atoms, an alkoxy radical containing 1 to 4 carbon atoms, a halogen atom, one of the following radicals a CO<sub>2</sub>-Q,



CH<sub>2</sub>-SQ in which Q and Q', identical or different, represent a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms, P, P' and P'', identical or different, represent an alkyl radical containing at most 4 carbon atoms, optionally substituted by one of the substituents indicated above for R and R', the symbol indicating that P and P' can optionally form, with the nitrogen atom to which they are linked, a heterocycle with 5 or 6 links.

5: R<sub>1</sub> and R<sub>2</sub>, identical or different, represent a hydrogen atom or an acyl group,

A and A', identical or different, represent a hydrogen atom, an equivalent of an alkali metal, an alkaline-earth metal, magnesium, ammonium or an amino organic base or A and A' represent the remainder of an easily cleavable ester group or CO<sub>2</sub>A represents CO<sub>2</sub><sup>⊖</sup>; the wavy line means that the CH<sub>2</sub>R<sub>1</sub> group can be found in E or Z position as well as the salts of the products of formula (I) with the mineral or organic acids, their preparation process, their use as medicaments, the compositions containing them and the new intermediates obtained.